ABN Abstracts

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001 WHEN AND HOW SHOULD NEUROLOGISTS TEST FOR MUTATIONS IN POLG?

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The production of adenosine triphosphate by mitochondrial oxidative phosphorylation is critically dependent on the structural integrity of the mitochondrial genome (mtDNA). mtDNA codes for 13 respiratory chain proteins which combine with over 70 nuclear subunits to form the final common pathway for energy metabolism. Until recently, it was thought that primary mtDNA mutations were the major cause of mitochondrial disease in adults, but an emerging class of autosomal mitochondrial diseases account for a rapidly growing clinical group: disease caused by mutations in POLG. POLG codes for the mitochondrial DNA polymerase g (polg), and POLG mutations cause disease through a secondary effect on mtDNA.

Here we present clinical and molecular data on more than 70 patients with POLG mutations. Although some developed classic features of mitochondrial disease, a large proportion had a common neurological disorder as the only feature for many years, including migraine, epilepsy, ataxia and parkinsonism. Some were identified through a systematic screen of spinocerebellar ataxia referrals, while others fulfilled diagnostic criteria for idiopathic Parkinson disease. Not all patients had abnormal muscle histochemistry, and multiple mtDNA deletions were not always detected in muscle. This presents a major diagnostic challenge, and referral for genetic testing ultimately depends on clinical intuition.

002 ADDENBROOKE'S COGNITIVE EXAMINATION-REVISED IN DAY TO DAY CLINICAL PRACTICE

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Objective: To report the diagnostic accuracy of the Addenbrooke's Cognitive Examination-Revised (ACE-R).
Methods/setting: Pragmatic prospective study of consecutive new referrals to a regional neuroscience centre, Cognitive Function Clinic, Liverpool, UK.
Results: Of 100 patients assessed (M:F 51:49; age range 24–85 years, mean age 60.9 (SD 11.6) years), 46 were judged to have dementia based on standard diagnostic criteria for dementia (DSM-IV), dementia subtype and mild cognitive impairment. 99 patients completed the ACE-R; scores ranged from 18 to 97. At the specified cut-offs (88, 82) sensitivity was comparable with that in the index paper (>90%) but specificity was lower (<75%). As there were no ''normals'' in this cohort, a lower cut-off was also examined (75) which improved specificity (>90%) without compromising sensitivity (>90%), positive predictive value approached 90% and likelihood ratios were moderate to large. Diagnostic accuracy, as measured by area under the receiver operating characteristic curve, was excellent (0.95, 95% CI 0.90 to 0.99).
Discussion/conclusion: ACE-R is easy to use and has excellent accuracy for the diagnosis of dementia. In day to day clinical practice, lower cut-offs may be preferable to those recommended in the index paper, perhaps reflecting the different casemix inherent when exclusion criteria (selection bias) are not applied.

003 GOOGLE NEUROLOGY: DOES IT HELP AND DOES EXPERIENCE MATTER?

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Introduction: Clinicians increasingly use the internet to explore a differential diagnosis. Google is the most often used search engine. This study investigated whether Google could help select the correct neurological diagnosis and whether this was influenced by clinical experience.
Methods: 20 random web published case reports were selected. The history and examination findings were provided to a FP1 (year 1 doctor), Senior House Officer (SHO) and Specialist Registrar (SpR). The doctors selected up to five search terms of their own choosing based on the history and examination. The most likely diagnosis was selected from the primary link of the first 20 Google hits obtained.
Results: Overall, in 14 (70%; 95% CI 49 to 90%) the correct diagnosis was selected from the Google search. Individually, the selected Google diagnosis was correct in 65% for the SpR, 35% for the SHO and 35% for the FP1. There was a significant difference between the average number of search term hits for a correct (3422 hits, SD 10278) compared with an incorrect (16050 hits, SD 34920) diagnosis ($p<0.05$).
Conclusion: Searching the internet using Google was helpful in establishing a neurological diagnosis. However, it still requires the clinician to select the appropriate search terms and analyse the subsequent information retrieved. The search was more successful when using specific search terms from examination findings. Google was more useful with increasing clinical experience.

004 RECOGNITION OF EMOTIONS IN FACES, VOICES AND MUSIC IN FRONTOTEMPORAL LOBAR DEGENERATION

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Frontotemporal lobar degeneration (FTLD) is a group of neurodegenerative conditions characterised by focal frontal and/or temporal lobe atrophy. Patients develop a range of cognitive and behavioural abnormalities, including prominent difficulties in comprehending and expressing emotions, with significant clinical and social consequences. Here we report a systematic prospective analysis of emotion processing in different input modalities in patients with FTLD. We examined recognition of happiness, sadness, fear and anger in facial expressions, non-verbal vocalisations and music in patients with FTLD and in healthy age matched controls. The FTLD group was significantly impaired in all modalities compared with controls, and this effect was most marked for music. Analysing each emotion separately, recognition of negative emotions was impaired in all three modalities in FTLD, and this effect was most marked for fear and anger. Recognition of happiness was deficient only with music. Our findings support the idea that FTLD causes impaired recognition of emotions across input channels, consistent with a common central representation of emotion concepts. Music may be a sensitive probe of emotional deficits in FTLD, perhaps because it requires a more abstract representation of emotion than do animate stimuli such as faces and voices.

005 ACCURACY OF SPECT IN DIFFERENTIATING FRONTOTEMPORAL DEMENTIA FROM ALZHEIMER'S DISEASE

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Objectives: Alzheimer's disease (AD) and frontotemporal dementia (FTD) are the commonest causes of presenile dementia. In the absence of a biological marker, diagnosis is reliant on clinical evaluation. Confirmation is often sought from neuroimaging, including single photon emission computed tomography (SPECT). Most previous SPECT studies lack pathological validation. The aim of this study was to examine the accuracy of SPECT in differentiating FTD from AD in patients with subsequent pathological confirmation.
Methods: 99mTc-HMPAO SPECT images obtained at initial evaluation in 25 pathologically confirmed cases of FTD were examined. These images were visually rated by an experienced blinded nuclear medicine consultant and compared with those of 31 patients with AD, also with pathological validation.
Results: A reduction in frontal cerebral blood flow (CBF) was more common in FTD and of diagnostic value (sensitivity 0.8, specificity 0.65 and +LR 2.25; CI 1.35 to 3.77). A pattern of bilateral frontal CBF reduction without

the presence of associated bilateral parietal CBF change is diagnostically more accurate (sensitivity 0.80, specificity 0.81 and +LR 4.13; CI 1.96 to 8.71). Diagnostic categorisation (FTD or AD) on SPECT alone was less accurate than clinical diagnosis (based on neurology and detailed neuropsychological evaluation). One FTD patient was initially misdiagnosed clinically as AD because of lack of availability of full neuropsychological assessment. However, SPECT correctly diagnosed this patient, providing a diagnostic gain of 4%.
Conclusion: 99mTc-HMPAO SPECT CBF patterns provide valuable information in the diagnosis of FTD and AD. These data are better used as an adjunct to clinical diagnosis if pathology is to be correctly predicted in life.

006 USEFULNESS OF A FIRST SEIZURE CLINIC: EPILEPTOLOGY MEETS AUDIT

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Rationale: In order to minimise the risk of misdiagnosis, guidelines have stressed the need for expert assessment of patients presenting with a first episode of blackout. We feel it is important to audit the diagnosis and investigation in use in this setting.
Methods: A prospective database monitored the initial diagnosis, eventual diagnosis and investigation results in 1038 patients attending a first seizure clinic.
Results: By December 2006, follow-up data were available for 1017 patients for between 1 and 47 months. 30% were initially thought to have syncope and 49% an ictal cause. Among those with an ictal cause, 266 (51%) had a sustainable diagnosis of epilepsy. A change in syndromic diagnosis was rare. Psychiatric or sleep related problems were diagnosed in 11%, with no definite pattern in 7%. Follow-up showed that diagnostic change was required in 3% of those with an initial diagnosis of syncope (all to a form of epilepsy) and 1% of those initially thought to have epilepsy.
Conclusions: A first seizure clinic is an excellent way of preventing misdiagnosis and appropriately targeting treatment and investigation. Failure to provide such resources will perpetuate the current poor state of long term epilepsy care in the community.

007 DISABILITY AND T2 MRI ABNORMALITIES: A 20 YEAR FOLLOW-UP OF PATIENTS WITH RELAPSE ONSET OF MULTIPLE SCLEROSIS

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Background: Many people who present with a clinically isolated syndrome (CIS) have MRI lesions suggestive of multiple sclerosis (MS).
Aim: To evaluate the relationship between the MRI lesions and clinical course over 20 years from CIS onset.
Methods: 89 CIS patients were followed-up after a mean of 19.6 years (range 17.6–22.6). MS was diagnosed clinically and disability determined by the Expanded Disability Status Scale (EDSS) and MS Functional Composite (MSFC).
Results: MS developed in 57/89 of patients; 51/59 with an abnormal and 6/30 with a normal baseline MRI scan. 33 developed relapsing remitting (RR) MS while another 24 went on to have secondary progressive (SP) MS. Median EDSS was 4.0. Baseline T2 lesion volume (LV) tended to be higher in SPMS ($P=0.09$). Baseline T2LV correlated moderately with EDSS ($rs=0.50$; $p<0.001$) and MSFC ($rs=-0.49$; $p<0.001$) after 20 years. The estimated rate of lesion growth in RRMS and SPMS was 0.79 cm^3 and 2.24 cm^3 per year, respectively. The difference of 1.45 cm per year was highly significant (95% CI 0.61 to 2.14; $p<0.001$).
Conclusion: Baseline T2LV at CIS onset correlates with disability after 20 years. Lesion load continues to increase for at least 20 years in relapse onset MS and the rate of lesion growth is higher in SPMS than in RRMS.

008 AUDIT OF NEW INPATIENT NEUROLOGY REFERRALS TO A DISTRICT GENERAL NEUROLOGY SERVICE: VALUE OF A CONSULTING NEUROLOGIST

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Altnagelvin Area Hospital is a 488 bed district general hospital serving the north west region of Northern Ireland providing general medical, surgical, paediatric and obstetric cover. A consultant neurologist was appointed in 2004.

An audit of new inpatient referrals to neurology was carried out over a 12 month time period from December 2005 to December 2006. 174 new patients were assessed and managed in tandem with the referring team.

Neurology input resulted in a change in diagnosis in 36.8% of consultations (64 cases) and a change in patient management in 59.2% (103). Only 1.7% (3 cases) remained without a diagnosis after neurology review. The neurological conditions, which relied more appreciably on specialist consultation for diagnosis, were neuromuscular (83% change in diagnosis) and non-organic (91.7% change in diagnosis). The referring teams had a high success rate in diagnosing more prevalent conditions such as cerebrovascular accident (46% change in diagnosis) and epilepsy (16% change); neurology contribution was notable for alteration in patient management in these cases. 74% of patients with cerebrovascular disease and 88.7% of patients with a diagnosis of epilepsy had their management changed in some way.

This audit outlines the important contribution of a specialist neurology service in a district general hospital in two major areas: (1) facilitation of diagnosis in specific neurological conditions and non-organic presentations; (2) highlights the benefit to referring teams of specialist involvement in patient management.

009 CHANGE IN DISABILITY IN PATIENTS WITH MULTIPLE SCLEROSIS: A 21 YEAR PROSPECTIVE POPULATION BASED ANALYSIS

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Introduction: Accumulation of disability in patients with multiple sclerosis (MS) is highly variable. Long term analysis of an unselected cohort is required to accurately determine the change in disability, and this information is of benefit in counselling patients, determining treatment strategies and allows resource planning.
Method: A cohort of prevalent patients in South Wales, identified in 1985, were traced using general practitioner and/or National Health Service databases. Those alive were examined and current disability determined and compared with that in 1985.
Results: 379 patients were included in the analysis. 214 (56.8%) patients had died. Expanded Disability Status Scale (EDSS) scores were available for 289 patients in 1985. Of these, 166 had died; EDSS scores were available in 103 patients and 20 were untraceable or declined. Mean EDSS change was 2.7 in surviving patients and 3.3 overall. Of those with EDSS <4 and 4–6 in 1985, 66.3% and 83.6%, respectively, required bilateral support or worse. 80.9% of those with EDSS ≥ 8 in 1985 had died. Of those not requiring assistance to walk in 1985, 20% were still ambulatory without assistance. However, 10.4% of the cohort had worsened by <1 point and 31/337 (9.1%) patients had an EDSS <4 at >21 years after disease onset.
Conclusion: 14.5% of patients with MS will have either benign or stable disease over the long term. Future analysis may allow the identification of predictive factors which together with awareness of the natural history of MS may be important for assessing the nature and risk of individual patient treatment strategies.

010 THE NEUROSCIENCE INTEGRATED CLINICAL ASSESSMENT AND TREATMENT SERVICE IN GREATER MANCHESTER: GRABBING THE BULL BY ITS HORNS

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Waiting lists for hospital treatment are a peculiarly British disease. The government has pledged a maximum wait of 18 weeks from referral to treatment by 2008. Procurement of additional capacity from independent sector providers and the introduction of a quasi-market through ''patient choice'' and ''payment by results'' will enable this target to be achieved.

Current developments offer the spectre of subspecialists assessing patients using radiology reported on foreign shores, with follow-up of chronic disease by general practitioners in the community.

These developments may threaten established neuroscience centres, but they also offer opportunities to access funds for additional facilities to achieve the 18 week target.

The Neuroscience Integrated Clinical Assessment and Treatment (ICAT) service has been set up to triage referrals, to provide scans and to offer clinic appointments as required.

Scanning is done independently of the National Health Service using the university scanner. Extra funding has been acquired for additional neurology and neurosurgery clinic capacity.

Time from referral to MRI scanning has fallen from 216 to 13.5 days. Time from referral to clinic appointment has fallen from 70 to 18 days. The ICAT will roll out across Greater Manchester over the next few years.

Our experience may be of interest to colleagues of a more paranoid predisposition.

011 OUTCOME OF TAILORED PSYCHOTHERAPY FOR NON-EPILEPTIC SEIZURES AND OTHER FUNCTIONAL NEUROLOGICAL SYMPTOMS

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Objectives: To assess whether individually tailored psychodynamic psychotherapy for patients presenting to neurology with functional symptoms is associated with improvements in self-reported measures of emotional well being, quality of life and somatic symptoms, and whether this treatment is cost effective.
Methods: Uncontrolled, prospective service evaluation in consecutive patients referred from neurology clinics to a single psychotherapist. Validated questionnaires used were Clinical Outcomes in Routine Evaluation Outcome Measure (CORE-OM), Short Function-36 Health Survey (SF-36) and Patient Health Questionnaire-15 (PHQ-15). Patients had a median of 6 treatment sessions (1–24). 91 patients completed questionnaires at referral, 63 at the end of treatment and 34 at the 6 month follow-up.
Results: Significant improvements were demonstrated on all measures and were maintained at follow-up (CORE-OM $p=0.003$, SF-36 $p<0.001$, PHQ-15 $p=0.001$). Significance was maintained in an intention to treat analysis. 49.2% of patients improved by at least 1 SD on at least one measure. The cost effectiveness of the intervention was estimated as £5328/quality adjusted life year.
Discussion: Individually tailored psychotherapy for patients with functional neurological symptoms was associated with significant improvements in patient centred measures at comparatively low costs. The results reinforce the need for a randomised controlled study of psychotherapy in this patient group.

012 DRPLA IN SOUTH WALES

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Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare autosomal dominant clinically heterogeneous neurodegenerative disorder characterised clinically by progressive dementia, ataxia, chorea, myoclonic epilepsy and psychiatric disturbance, and pathologically by combined degeneration of dentatorubral and pallidoluysian systems. DRPLA has a marked ethnic predilection and is most commonly reported in Japan and is rare in Caucasian populations.

We describe 13 affected individuals within five families from South Wales, with a video demonstration of the clinical findings and marked variability. Age at onset ranged from 34 to 60 years, with an earlier onset associated with myoclonic epilepsy and then development of dysarthria, ataxia and chorea. Late onset patients presented with a Huntington disease-like picture with chorea and dementia. Two patients presented with gait ataxia but in both cases this had been preceded by psychiatric symptoms up to 15 years earlier.

To investigate the origins of expanded DRPLA alleles in South Wales, we studied repeat length polymorphism in 306 Welsh control patients. We identified 14 (4.6%) control patients with repeat lengths in the high–normal range, compared with 0% and 7.4% in previously reported North American Caucasian and Japanese control populations, respectively. The high prevalence of high–normal length alleles may account for the high prevalence of DRPLA in Wales.

013 CRITICAL CAP THICKNESS AND RUPTURE IN SYMPTOMATIC CAROTID PLAQUES: THE OXFORD PLAQUE STUDY

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Background: Coronary atherosclerotic plaques with a fibrous cap thickness <65 μm are prone to rupture but the critical cap thickness for a carotid plaque is unknown.
Method: We made detailed histological assessments of 526 plaques from consecutive patients undergoing endarterectomy for symptomatic carotid stenosis. Minimum and representative cap thicknesses were compared in ruptured and non-ruptured plaques.
Results: Median representative cap thickness was 400 μm (IQR 220–600) and the median minimum cap thickness was 200 μm (100–300). There was a strong inverse relationship between cap thickness and cap rupture ($p<0.001$). The optimum cut-off cap thickness values for predicting cap rupture were a minimum cap thickness <200 μm and a representative cap thickness <460 μm. Plaques with a minimum cap thickness <200 μm and cap rupture had a higher prevalence of marked cap inflammation compared with plaques with thick (minimum cap $\geqslant 200$ μm) and intact caps (OR 9.26, 5.00–17.15, $p<0.001$).
Conclusion: Carotid plaques are prone to rupture at a greater cap thickness than coronary plaques. A minimum cap thickness of <200 μm identifies ruptured carotid plaques most reliably. Current imaging techniques should aim for this resolution in order to reliably identify vulnerable carotid plaques on the basis of cap thickness.

014 NEUROPROTECTIVE AUTOIMMUNITY FOLLOWING CAMPATH-1H TREATMENT OF MULTIPLE SCLEROSIS

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Autoimmunity is generally considered detrimental. In multiple sclerosis (MS), autoaggressive T cells lead to demyelination and acute axonal transection. Recent evidence indicates, however, that autoimmunity can be beneficial through the production of neurotrophic factors. This is termed neuroprotective autoimmunity.

Treatment with the monoclonal antibody Campath-1H induces prolonged T cell lymphopaenia and reduces the relapse rate by 90% (or by $>70\%$ compared with interferon-beta). Unexpectedly, patients with relapsing remitting MS show a sustained improvement in disability for at least 24 months. This has not been reported in trials of other MS therapies.

We hypothesised that immune cells, regenerated after Campath-1H, secrete factors which promote neuronal and oligodendrocyte survival.

Using ELISA, we demonstrated that patients' peripheral blood mononuclear cells (PBMC) in culture with myelin basic protein secrete increased levels of brain derived neurotrophic factor and ciliary neurotrophic factor after Campath-1H. Increased mRNA levels of these factors, in addition to neurotrophic factor-3 and nerve growth factor, were also observed. Furthermore, post-treatment derived PBMC conditioned medium was found to support the survival of rodent neurons, and the survival and maturation of oligodendrocyte precursor cells in vitro.

This study suggests that Campath-1H promotes neuroprotective autoimmunity by increased lymphocytic production of neurotrophic factors. These findings may, in part, explain the improvement in disability seen post treatment.

015 ANTIBODIES TO CLUSTERED ACETYLCHOLINE RECEPTOR AND THYMIC CHANGES IN SERONEGATIVE MYASTHENIA GRAVIS

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Patients with generalised myasthenia gravis (MG) who are negative for acetylcholine receptor (AChR) and muscle specific kinase (MuSK) antibodies by standard assays (seronegative MG, SNMG) often present with similar clinical manifestations, treatment responses and thymic pathology to those patients with AChR antibodies, and differ from those with MuSK antibodies. We hypothesised that SNMG patients have low avidity antibodies that only bind to AChR at high density, such as at the neuromuscular junction. We studied the earliest serum/plasma samples available from 41 SNMG patients. We first expressed AChRs in a mammalian non-muscle cell line and found only weak binding of IgG by immunofluorescence. However, when we clustered the AChR using the intracellular protein rapsyn, there was strong binding of IgG in 27/41 SNMG sera. Moreover, this IgG antibody to clustered AChR correlated with the presence of thymic lymphocytic infiltrates and deposits of complement C3 on myoid cells nearby, suggesting involvement of the thymic myoid cells in the development of these antibodies. Overall these findings provide the first clear demonstration of IgG antibodies to AChR in many of the previously seronegative patients, and the likelihood of similar pathogenic mechanisms shared between ''SNMG'' and AChR antibody positive patients.

016 AN INVESTIGATION OF GANGLION CELL LOSS IN RETROGENICULATE HEMIANOPIA USING OPTICAL COHERENCE TOMOGRAPHY

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Background: There is experimental evidence of trans-synaptic retrograde degeneration (TRD) of retinal ganglion cells following retrogeniculate lesions in animals but the findings of acquired lesions in human have been controversial.
Objective: To compare the peripapillary retinal nerve fibre layer thickness (RNFT) in cases of hemianopia.
Methods: The RNFT was measured using optical coherence tomography. We recruited 12 cases of acquired homonymous hemianopia (AHH) and 7 cases of congenital homonymous hemianopia (CHH). There were 11 controls.
Results: There were significant differences in mean RNFT bilaterally between AHH and controls, and between CHH and controls. The control group had the thickest mean RNFT. A significant difference in the mean RNFT between AHH and CHH was detected only in uncrossed fibre defect eyes. ''Band atrophy'' patterns were observed in the crossed fibre defect eyes and were found to involve superior and inferior arcuate bundles in the fellow eyes in AHH and CHH. The temporal quadrant appeared to be affected bilaterally.
Conclusion: Thinning of the peripapillary retinal nerve fibre layer was seen in both congenital and acquired post-geniculate lesions, in a general pattern predictable from the known nerve fibre trajectories. This study is the first direct confirmation of TRD in acquired damage to the human visual pathway.

017 MOTIVATION AND LEARNING IN THE BASAL GANGLIA

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The past few years have seen a remarkable evolution in our understanding of dopamine and basal ganglia function, with insights originating from sometimes surprising sources, such as engineering and economics. Contemporary theories have revealed a much broader picture than previously recognised—one that integrates a diversity of cognitive and emotional processes with action learning and motivational control, with substantial implications for our understanding of basal ganglia disorders and their treatment.

We present experimental findings from human behavioural, pharmacological and neuroimaging studies of motivational learning and decision making that illustrate key new findings and inform recent theoretical models. Firstly, we show that the striatum is involved in learning about both reward and aversive events such as pain, suggesting that it integrates motivational signals across the spectrum of rewards and punishments. Secondly, we show that the striatum has a highly specific role in learning about novelty, highlighting a critical role in guiding exploratory behaviour. Lastly, we show that dopamine modulates a striatal reward prediction error signal during gambling tasks.

These results embellish reinforcement learning theoretic models of basal ganglia function, and offer formal accounts of several well recognised features of basal ganglia dysfunction, including pathological gambling in Parkinson disease.

018 MUTATIONS IN MITOFUSION 2 ARE A COMMON CAUSE OF CMT2

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Charcot-Marie-Tooth disease (CMT) is a genetically and clinically heterogeneous disorder and to date about 26 genes have been isolated. CMT is generally classified as type 1, the demyelinating form (CMT1), or type 2, the axonal form (CMT2). To date, no major gene for CMT2 has been identified. Recently, mutations in mitofusin 2 (MFN2) have been identified as a common cause of CMT2. MFN2 is a mitochondrial membrane protein that is crucial for mitochondrial fusion. 67 patient samples were analysed by sequencing the 17 coding exons of the MFN2 gene. A mutation in the MFN2 gene was found in 15% of patients. The majority of mutations found were novel. All patients had an axonal neuropathy, one also had optic neuropathy and some were more severe than typical CMT2. Two cases will be presented. Mutations in MFN2 are a significant cause of CMT2. MFN2 should be the first gene screened in autosomal dominant and sporadic CMT2 patients.

019 ATYPICAL PRESENTATION OF VARIANT CREUTZFELDT–JAKOB DISEASE IN A 73-YEAR-OLD TRANSFUSION RECIPIENT

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We report atypical presentation of variant Creutzfeldt–Jakob disease (vCJD) in a 73-year-old transfusion recipient. This individual was transfused following surgery in December 1997. Tracing of products identified 1 unit of non-leucodepleted red cells from an individual who developed symptoms of neuropathologically confirmed vCJD 21 months after donation. The recipient was offered specialist investigation at the National Prion Clinic in March 2006. At this time, the patient was asymptomatic and neurological examination was unremarkable. MRI brain demonstrated no thalamic signal change. Progressive symptoms emerged 4 months later with imbalance and deteriorating cognition. Examination 2 months after onset of symptoms demonstrated marked cognitive impairment alongside cerebellar signs, including impaired manual dexterity and ataxic gait. Serological investigations were normal. Neuropsychometry confirmed prominent frontal and temporal deficits. Repeat MRI brain demonstrated no thalamic signal change. PRNP genotyping revealed no mutations and homozygosity for methionine at codon 129. The patient failed to fulfil the WHO diagnostic criteria for vCJD; nevertheless, a tonsil biopsy confirmed the presence of pathological prion protein by immunohistochemistry and western blot. This case emphasises the significant risk of vCJD encountered by recipients of contaminated blood products and highlights how patients may present with an atypical phenotype. Tonsil biopsy facilitates timely diagnosis of vCJD

020 INCLUSION BODY MYOPATHY WITH PAGET'S DISEASE OF BONE AND FRONTOTEMPORAL DEMENTIA: CLINICAL FEATURES OF A LARGE PEDIGREE

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Background: Autosomal dominant inclusion body myopathy (IBM) associated with Paget's disease of bone (PDB) and frontotemporal dementia (FTD), or IBMPFD, is a recently described disorder whose clinical features are not well described.
Objective: To review the clinical, radiological and pathological features of patients with IBMPFD caused by a known mutation of valosin containing protein.
Methods: The clinical features of 12 patients in a large pedigree with IBMPFD were reviewed along with radiological, neurophysiological and pathological data.
Results: 20 patients with IBMPFD were identified in the family of which four were examined carefully. Mean age of onset of muscle symptoms was 34 years (range 20–49), usually leading to wheelchair dependence. Three subjects interviewed had bladder symptoms, erectile failure or faecal incontinence. Four subjects had evidence of cardiomyopathy. Paget's disease was present asymptomatically in two subjects. Left temporal lobe atrophy and cord atrophy was seen on MRI in an older patient with clinical evidence of FTD. Muscle biopsy also had variable features of IBM and denervation.
Conclusion: IBMPFD is a multisystem disorder that may imitate a number of other neuromuscular conditions and which may be associated with sphincter disturbance in addition to clinical features already recognised.

021 COPPER DEFICIENCY MASQUERADING AS SUBACUTE COMBINED DEGENERATION OF THE CORD AND MYELODYSPLASTIC SYNDROME

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A 69-year-old man, who had undergone partial gastrectomy 40 years previously, presented with anaemia and leucopenia. Bone marrow histology suggested myelodysplasia and repeated palliative transfusions were given.

He subsequently developed a progressive spastic paraparesis with marked dorsal column involvement, losing independent mobility within 12 months. Early imaging was normal but a later MRI demonstrated a longitudinal posterior cord lesion suggestive of subacute combined degeneration. Despite extensive investigation, including B12 assay, no cause was identified until copper and caeruloplasmin were found to be undetectable. Oral copper supplementation (8 mg/day) resulted in prompt haematological recovery and cessation of neurological deterioration.

Copper is a ubiquitous micronutrient essential to the function of the nervous system and bone marrow. Daily requirements are low but acquired deficiency has recently been recognised as a rare cause of myeloneuropathy and a haematopoietic disorder mimicking myelodysplasia.

Prompt recognition and treatment allows complete reversal of the haematological abnormalities and arrest of the neurological decline, which is otherwise often irreversible despite supplementation.

This entity represents a rare but completely treatable cause of potentially devastating neurological disability which should be considered in individuals presenting with undiagnosed myelopathy. The coexistence of haematological abnormalities and a history of gastric surgery may point to the diagnosis.

022 TALL, MYOPIC, PULSELESS, DROWSY AND A ''STROKE'' OF LUCK

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The diagnosis of venous sinus thrombosis confirmed on CT, after a 3 day history of headache, nausea and drowsiness in a 17-year-old female taking the oral contraceptive pill, prompted further investigation after symptoms of intermittent leg claudication and findings of absent peripheral pulses.

Despite studying eight GCSEs, wearing glasses since childhood, two previous bony fractures and being on the 97th height centile, the presence of irregularly narrowed external iliac arteries on CT angiogram together with the recent history of a venous thrombotic event raised the possibility of a metabolic cause for this combination of venous and arterial occlusion.

The diagnosis of homocystinuria was confirmed with plasma total homocysteine 350 μmol/l (<16 μmol/l), with increased methionine 312 μmol/l (15–40) and with low plasma cysteine 41 μmol/l (48–90). Ophthalmic review confirmed high myopia, lens subluxation and macular striae. Management continues with warfarin, pyridoxine, oral vitamin B12, folic acid and betaine.

Thromboembolism and atherosclerosis are the main causes of morbidity and mortality in homocystinuria but rarely is vascular occlusion the presenting manifestation that leads to its investigation.

This case illustrates how homocystinuria, as a potentially treatable and modifiable condition, may remain undiagnosed until the occurrence of a catastrophic event or even a ''stroke'' of luck.

023 A SERIES OF UNFORTUNATE EVENTS

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A 35-year-old woman with a past history of breast cancer became unwell with nausea, sickness, fatigue and progressive confusion. A diagnosis of Addison's disease was made and she improved with steroid replacement and electrolyte correction. One week after commencing treatment she developed a progressive akinetic–rigid syndrome with bilateral resting tremor. She became mute and, within 5 days, was completely immobile and required ventilation. CSF examination and initial MRI were normal and she was treated with immunotherapy for a presumed paraneoplastic disorder. Repeat MRI after 2 weeks revealed high signal changes in the basal ganglia, consistent with extrapontine myelinolysis. She was treated with levodopa and made a full clinical recovery after several months.

CNS myelinolysis should be suspected in patients with rapid correction of hyponatraemia. It predominantly affects areas of compact interdigitation of grey and white matter and can occur without pontine involvement. Initial imaging is often normal.

024 TREATABLE MILLS SYNDROME: A UNIQUE CASE OF COELIAC DISEASE MIMICKING MOTOR NEURONE DISEASE

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A 44-year-old male presented with a 6 month history of progressive right leg then right arm weakness. Examination revealed a wasted right thigh, spastic right hemiparesis, a right extensor plantar and widespread hyperreflexia (video). Sensory testing was normal. Electromyography, including the masseter, revealed widespread denervation. MRI demonstrated non-enhancing T2 hyperintensity of the left motor cortex and descending corticospinal tract, later spreading to involve the right motor cortex. Cerebrospinal fluid constituents were normal with no oligoclonal bands detected. HIV and JC virus serology were negative.

A mild microcytic anaemia with low serum iron and folate levels were found. Antiendomysial antibody testing was positive, and duodenal biopsy was consistent with gluten enteropathy. Six months after commencing a gluten-free diet, the patient showed improved gait and was able to resume writing.

Ataxia is the most common neurological manifestation of coeliac disease although axonal motor neuropathy is described. The clinical syndrome of progressive hemiparesis with preserved sensation was first described by Mills and can be a rare phenotype of motor neurone disease. The EMG abnormalities and corticospinal tract hyperintensity initially supported this hypothesis. The ongoing improvement with a gluten-free diet suggests that the Mills' phenotype be added to the potential neurological manifestations of coeliac disease.

025 INCIDENCE OF DEMENTIA AND FACTORS PREDICTING COGNITIVE DECLINE IN PARKINSON DISEASE

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In order to investigate the evolution of cognitive dysfunction in early Parkinson disease (PD), we prospectively assessed an incident community based cohort of 126 patients (diagnosed according to UKPDS Brain Bank criteria) at presentation and 3–5 years later using a comprehensive clinical and neuropsychological battery. Genotyping was performed for common variants in genes implicated in protein aggregation (MAPT, SNCA) and dopaminergic regulation (COMT, BDNF). 9% of patients developed dementia over a mean (SD) follow-up period of 3.5 (0.7) years, corresponding to an annual dementia incidence of 25.9 (12.9, 46.5) per 1000 person years of observation. A non-tremor dominant motor phenotype, and performance on two simple cognitive tasks at baseline (semantic fluency and pentagon copying), predicted rate of cognitive decline (change in Mini-Mental State Examination per year) following adjustment for age. While genes involved in dopaminergic regulation were not associated with cognitive decline, MAPT genotype was a significant predictor of cognitive decline and dementia risk. Our findings suggest that the dementia of PD has a posterior cortical rather then dopaminergic frontostriatal basis. Furthermore, this work has identified early markers of dementia which could ultimately enable better therapeutic and supportive strategies to be adopted at a time when they are most likely to be effective.

026 COMPARISON OF DATSCAN IMAGING AND SMELL TESTING IN ESSENTIAL TREMOR AND PARKINSON DISEASE

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Background: Parkinson disease (PD) is commonly misdiagnosed for essential tremor (ET), especially early in the diagnosis. Usually, DaTScan is normal in ET and abnormal in PD. Smell identification is frequently impaired in PD and intact in most cases of ET.

Methods: We recruited 57 patients with tremor or PD. Follow-up duration was 8–36 months. A final clinical diagnosis of ET was made in 22/57 by TRIG (Tremor Investigation Group) criteria and PD in 35/57 by UKPD brain bank criteria. All subjects had: (1) Mini-Mental Status Examination scores ⩾27/30; (2) University of Pennsylvania Smell Identification Test (UPSIT); (3) [123I]b-FP-CIT DaTscan analysed by QuantiSPECT. For controls, we used 15 healthy subjects who underwent all three tests.
Results: 35 PD: mean age 65.4 years; 22 ET: mean age 64.5 years; 15 controls: mean age 64.7 years. Mean UPSIT scores: 32.5/40 in ET (SD 4.0), 33/40 in controls (SD 4.9) and 17.7 in PD (SD 6.8; $p<0.001$ compared with ET and controls). Average striatal uptake was significantly lower in PD (3.95 (1.30)) compared with ET (5.51 (0.94); $p<0.001$) and controls (5.80 (0.62); $p<0.001$).
Conclusion: We confirmed that both DaTScan and olfactory function are abnormal in PD and normal in ET. There were highly significant differences between ET and PD on both UPSIT and DaTScan. There was a strong and consistent relationship between DaTscan, odour identification and the final clinical diagnosis.

027 A CLINICAL, GENETIC AND ELECTROPHYSIOLOGICAL STUDY OF A NEW UK EPISODIC ATAXIA TYPE 1 PEDIGREE

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Episodic ataxia type 1 (EA1) is a rare autosomal dominant disorder characterised by brief attacks of ataxia on a background of continuous myokymia, caused by mutations in the voltage gated potassium channel, KCNA1. Seventeen mutations are described. These mutant channels show reduced potassium current density as well as other subtle effects on channel function. However, the biophysical consequences have mainly been studied in Xenopus laevis oocytes, which do not always reproduce mammalian cell biology. Therefore, we decided to analyse EA1 mutations in human cells to measure whether the differences observed are consistent with those seen in oocytes.

All members of the pedigree were examined by one investigator and underwent digital video recording and EMG examinations. The entire KCNA1 gene was directly sequenced. A novel missense mutation, F414S, was identified. This was inserted into a cDNA construct of KCNA1 contained within the mammalian expression vector, pcDNA3+, using site directed mutagenesis. Human embryonic kidney (HEK-293) cells were transiently transfected using standard techniques. Potassium currents were measured using whole cell patch clamp recordings with potassium gluconate based internal solution and standard mammalian Ringer's solution. Mutant potassium channels showed a reduced current density in addition to a right shift in voltage dependence of activation compared with wild-type channels.

028 THE TALKING WOUNDED: CONVERSATION AND LANGUAGE TESTING IN PROGRESSIVE APHASIA

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A quarter of a century has passed since Mesulam's original description of progressive aphasia, but although ''fluent progressive aphasia'' has now been characterised as the well defined clinicopathological syndrome of semantic dementia, the remaining patients, labelled ''progressive non-fluent aphasia'' (PNFA), are less well described. Indeed, it remains debatable whether these patients form a coherent group.

We studied 15 subjects with PNFA and 15 age matched controls by analysis of their conversational speech and by neuropsychological testing. As a group, the patients' speech was slow and errorful, with word finding difficulty, short phrases and simplified grammar. In parallel, most patients showed deficits on tests of naming, phonology and syntax comprehension, with word–picture matching consistently spared. Surprisingly, the single most consistent deficit was on a non-verbal test of frontal lobe function, the Wisconsin card sort test.

While there were significant differences in emphasis between individuals, the data did not in general suggest clear divisions into sub-syndromes. However, poorly articulated speech and poor phonological short term memory were strongly associated, and appeared to dichotomise the group. PNFA remains a useful label, but further work is necessary to explore the functional and pathological importance of the articulation–STM split.

029 RELATING THE USE OF MEMORY AIDS TO MEMORY PERFORMANCE

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Background: Complaints of memory loss are a common cause of attendance at general practice surgeries and specialist clinics. However, distinguishing complaints related to normal aging from those associated with early Alzheimer's disease can be problematic. Although many of these patients use memory aids (eg, diaries and calendars), it is uncertain whether this affects the likelihood of poor performance on tests of memory.
Methods: 56 patients with symptoms of memory loss were recruited from a memory clinic. Both patients and informants rated the patient's memory loss and use of memory aids. All patients subsequently underwent MRI scanning and neuropsychological testing.
Findings: (i) Poor performance on tests of memory was associated with decreased use of memory aids and recent onset of memory symptoms. (ii) Informant, but not patient, ratings of memory were associated with performance on tests of memory function and correlated with hippocampal size on MRI. (iii) The history from a close informant was more strongly predictive ($p=0.0002$) of cognitive impairment than subjective symptoms, use of memory aids or duration of symptoms.
Interpretation: In a clinical setting, information gathered from the history correlates with cognitive impairment on memory testing and brain appearances on MRI. The history from a close informant is particularly important.

030 INHERITED PRION DISEASE WITH THE P102L MUTATION: UPDATE OF A WORLDWIDE KINDRED ORIGINATING IN ENGLAND AND MULTIPLE UNRELATED EUROPEAN KINDREDS

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We present clinical data and an expanded family tree for the largest inherited prion disease kindred yet reported carrying the P102L mutation, originating in the UK. Included are five smaller unreported family branches only now demonstrated to be related to the large kindred and a further eight small unrelated P102L kindreds, suggesting multiple separate mutational events. The large family was one of two in whom PRNP point mutations were first identified. Clinical data demonstrated remarkable phenotypic heterogeneity. A subset of patients presented with predominantly cognitive and psychiatric features differing from the Gerstmann–Straüssler–Scheinker syndrome classically associated with P102L. Methionine homozygotes for the codon 129 polymorphism have an earlier mean age at onset than methionine/valine heterozygotes (47 vs 54, $p=0.04$ one tailed t test). Eight cases with the youngest onset ($n=30$ with codon 129 data) were all methionine homozygotes. Two sets of identical twins are presented as well as the youngest case reported so far, presenting with generalised dystonia. The many untraced members of the kindred whose descendents may be unaware of their at risk status raise public health concerns in view of the transmissibility of prion diseases. Undiagnosed sufferers would benefit from diagnostic certainty, especially as therapeutic trials in human prion disease begin.

031 DEVELOPMENTAL CHANGES IN WHITE MATTER MICROSTRUCTURE IN ADOLESCENCE

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Myelination in the brain is not fully completed during childhood. In order to understand normal development and study disease processes and treatment responses, we aimed to study age related structural white matter changes in healthy adolescents and young adults.

Diffusion tensor imaging (DTI) scans were performed on 42 adolescents and 20 young adults. Correlations between DTI parameters and age were calculated using a novel DTI technique called tract based spatial statistics.

Across the whole white matter, age was correlated with mean fractional anisotropy (FA) ($r=0.42$, $p<0.01$) and perpendicular eigen values ($r=-0.035$, $p<0.02$) in adolescents but not in young adults. Voxel-wise analysis showed localised positive correlations between age and FA in adolescents within two white matter regions: right body of the corpus callosum and right superior region of the corona radiata, and in young adults within the right superior longitudinal fascicle.

Our results suggest that widespread developmental changes in white matter microstructure continue throughout adolescence, are prominent in specific fibre pathways and may be driven by changes in both axonal membranes and myelin sheaths. White matter changes plateau in early adulthood with the exception of the cortical projection pathways travelling through the superior longitudinal fascicle.

032 POST-BONE MARROW TRANSPLANT LEUKOENCEPHALOPATHY

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A 39-year-old man had an allogenic bone marrow transplant (BMT) in October 2005 for follicular non-Hodgkin's lymphoma grade IIIB. Post-transplant complications included graft versus host disease (GVHD) of the gastrointestinal tract, aspergillus lung infection with pseudomonas colonisation, and Herpes simplex stomatitis resistant to treatment with acyclovir and famciclovir.

Six months after BMT he presented with a 14 day history of involuntary leg movements and two episodes of urinary incontinence. He had a left hemiparesis and was ataxic. MRI brain demonstrated non-enhancing confluent white matter high signal on T2 and FLAIR images in the deep and subcortical white matter and basal ganglia. CSF was acellular, with negative studies for bacterial and fungal culture, cryptococcal antigen, Herpes simplex virus (HSV), varicella zoster virus, cytomegalovirus and JC virus PCR.

Autopsy neurohistology confirmed multiple white matter, thalamic and brainstem necrotising lesions. There was no evidence of infarction, trauma, demyelination, lymphoma, bacterial or fungal infection. Lesions showed strong HSV immunopositivity.

This pattern of post-BMT brain damage has been reported previously, but its aetiopathogenesis has remained obscure. This case raises the possibility that at least some cases may represent an atypical presentation of HSV encephalitis, modified by associated immunosuppression and GVHD.

033 MOUSE ACROSS THE FLOOR SYNDROME: HALLUCINATIONS AND COGNITION IN PARKINSON DISEASE

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Objective: To determine the prevalence and detailed phenomenology of hallucinations in idiopathic Parkinson disease (IPD).
Methods: 203 consecutive IPD patients were screened for the presence of hallucinations using the Rush Hallucinations Inventory, Neuropsychiatry Inventory and Cambridge Cognitive Screen (CAMcog). Patients were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), PDQ 39, Beck's Depression Inventory II, Folsteins's Mini-Mental State Examination and Clock Drawing Test.
Results: 20 patients were identified as hallucinators. Male to female ratio was 2:1. Mean age was 62 years (range 59–78). Mean total UPDRS score was 56 (range 24–99) and mean motor score was 33 (range 9–64). Visual passage hallucinations were most frequent, followed by auditory (40%), sensory (20%) and olfactory (0.5%). Interestingly, 40% described visual errors of a mouse running across the floor. Insight was preserved in all cases.
Conclusion: Visual hallucinations in IPD patients may occur as a combination of executive dysfunction and perceptual processing deficits of external stimuli. Seeing a ''mouse running across the floor'' was a recurring theme and could possibly be used as a screening question for detecting hallucinations. But, as one patient confirmed, all incidences may not be hallucinations as he fed the mouse to the cat!

034 MEDICAL KNOWLEDGE OF DVLA GUIDELINES IN COMMON NEUROLOGICAL CONDITIONS: A COMPARATIVE STUDY

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Aims: Previous research has suggested that medical knowledge of the restrictions of the Driver and Vehicle Licensing Agency (DVLA) is patchy. The importance of accurate documented advice has legally never been greater. We aimed to ascertain, using 10 common neurologically based scenarios, whether junior medical doctors provide adequate advice compared with middle grade neurological trainees and highlight deficiencies in one or both groups.
Methods: Ten multiple choice questions outlining scenarios were distributed to junior doctors in three district general hospitals in Sussex ($n=36$) and a randomly selected group of London neurology SpRs ($n=19$) and were completed without advance warning.
Results: Mean scores were (out of 10): non-neurological juniors 5.0, neurology SpRs 6.8 (significant difference $p<0.01$). The question answered well by both groups was regarding first fit, while scenarios detailing provoked seizure and head injury were answered poorly by both groups. Neurology SpRs were significantly better on advising on cerebrovascular accident and vasovagal attack. No responder gained a maximum score.
Discussion: As expected, neurology SpRs offered more accurate advice and in certain situations were significantly better than their non-neurological colleagues although it is interesting to note that in some scenarios the response from both groups was deficient. This study suggests all doctors would benefit from continued education in medicolegal questions.

035 PREVALENCE AND GEOGRAPHICAL DISTRIBUTION OF UK CONGENITAL MYASTHENIC SYNDROME PATIENTS REFERRED TO THE OXFORD NATIONAL SPECIALIST COMMISSIONING ADVISORY GROUP SERVICE

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Congenital myasthenic syndromes (CMSs) are rare but their recognition is increasing as new mutations and phenotypes are characterised. We report the prevalence and geographical distribution of CMS patients referred to the Oxford National Specialist Commissioning Advisory Group (NSCAG) CMS service.

Of 210 UK CMS patients referred, we identified mutations in 131. Hence the overall UK prevalence is 2.2/million of genetically confirmed cases but this varies between strategic health authorities from 0.59 to 4.2/million. Racial clustering did not fully explain these geographical variations. The populations served by major neuromuscular centres had a higher prevalence (eg, Oxfordshire 13/million overall) than those without, and may more accurately reflect the true UK prevalence because of more complete case ascertainment.

The greater number of patients diagnosed recently with the newly identified Rapsyn mutations than with the commoner acetylcholine receptor e-subunit mutations suggests that there are likely to be many patients with Rapsyn mutations who remain undiagnosed currently, implying that the prevalence of genetically characterised CMS will continue to rise.

Our data suggest that the UK prevalence of CMS is much higher than previously suspected and that accurate diagnosis of rare syndromes such as CMS depends on access to local regional specialist units and subsequent referral to national diagnostic units such as those supported by NSCAG.

036 THYMECTOMY IN THE MANAGEMENT OF MYASTHENIA GRAVIS: THE WEST OF SCOTLAND EXPERIENCE

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We retrospectively studied a consecutive series of 66 patients with myasthenia gravis (MG) who underwent thymectomy between January 1992 and March 2006. Thymectomy was performed by a single operator using a ''limited'' trans-sternal technique. This study sought to ascertain the mortality and morbidity associated with this procedure, patients' improve-

ment in clinical outcome, as determined by the Myasthenia Gravis Foundation of America (MGFA) clinical score, and their long term requirement for immunosuppressive treatment. In our cohort, 44 patients were female and 52 patients were positive for acetylcholine receptor antibodies. The mean duration of disease before thymectomy was 2.5 years, mean age at thymectomy was 41.7 years and mean duration of follow-up after thymectomy was 4.5 years. The procedure was associated with minimal complications and there was no associated mortality. Postoperatively, 59% of patients achieved remission and the MGFA score at the final recorded end point was significantly lower than the maximal MGFA score before thymectomy ($p<0.0001$). After thymectomy, 26% of MG patients were on corticosteroids while 47% were receiving azathioprine. Our study confirms that ''limited'' transsternal thymectomy is associated with a low rate of postoperative complications and a favourable outcome in the clinical status of MG patients.

037 AETIOLOGY, TREATMENT AND OUTCOME OF NON-TRAUMATIC MYELOPATHY IN NORTHERN TANZANIA

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Background: Few data are available on non-traumatic myelopathy (NTM) in resource-poor settings.
Aims: To analyse the aetiology, treatment and outcome of NTM in such a setting.
Methods: Retrospective analysis of 84 consecutive adults with NTM over an 18 month period (October 2003–March 2005) in a referral hospital in Northern Tanzania.
Results: Age ranged from 15 years upwards. Male:female ratio was 58:26. A definite or strongly suspected aetiology was determined in 65 of 84 cases: neoplasia 16, tuberculosis (TB) 11, degenerative disorders 11, HIV related 10, transverse myelitis 4, B12 deficiency 3, Devic disease 2, epidural abscess 2, neurofibromatosis 2, other 4 and unknown 19. Medical treatments were: B12 in 42, anti-TB therapy in 27, prednisolone or dexamethasone in 27, praziquantel in 15, antibiotics in 10, vitamin E in 8, multivitamins in 5, pyridoxine in 4, spinal surgery in 4 and antiretroviral drugs in 3. Eleven had either no or undocumented treatment. At follow-up, 36 patients were unchanged, 19 had improved, 7 had died, 2 had deteriorated, 2 were referred elsewhere and the outcome not documented in 18.
Conclusions: Despite resource limitations, the aetiology of NTM was determined in most patients, with more than 50% accounted for by neoplasia, TB, degenerative disorders and HIV. Treatments varied, and the often broad based therapeutic approach appears justified as almost 25% of patients had improved at follow-up.

038 UNUSUAL MRI FINDINGS IN A PATIENT WITH *E COLI* 0157 INFECTION

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A 37-year-old female with a past medical history of Crohn's disease presented with a 10 day history of bloody diarrhoea. After initial clinical improvement with antibiotics and intravenous hydrocortisone, she developed oliguria and mild confusion. An elevated creatinine and mild thrombocytopenia were found, and stool culture was positive for *Escherichia coli* 0157. A diagnosis of haemolytic uraemic syndrome was made. With conservative treatment both renal function and platelet count began to improve.

However, 2 days later she developed expressive dysphasia, Parinaud's syndrome (including convergence–retraction nystagmus) and generalised seizures. MRI revealed symmetrical T2 weighted hyperintensity in the caudate tails, thalamic/subthalamic nuclei and periaqueductal grey. There was no evidence of cerebral venous thrombosis on MR venography, nor were there any cortical changes to support a diagnosis of thrombotic thrombocytopenic purpura (TTP). TTP blood protease testing was also normal.

Plasma exchange and intravenous thiamine were commenced empirically. The patient improved clinically over the next 3 weeks.

The highly unusual MRI findings are felt to represent a direct *E coli* 0157 enterotoxin related encephalopathy, or a post-infectious autoimmune process.

039 A NOVEL MITOCHONDRIAL TRNAPRO MUTATION ASSOCIATED WITH MYOCLONIC EPILEPSY WITH RAGGED RED FIBRES AND OTHER NEUROLOGICAL FEATURES

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We describe a 53-year-old woman with a novel mitochondrial (mt) tRNA mutation who presented with myoclonic epilepsy, deafness, cataracts, pigmentary retinal changes, myopathy, progressive ataxia and a maternal family history of diabetes. Muscle biopsy revealed 10% cytochrome c oxidase (COX) deficient fibres, some of which demonstrated a subsarcolemmal distribution of abnormal mitochondria, and decreased activity of respiratory chain complex I. Common mtDNA mutations were absent in muscle, prompting sequencing of the entire mitochondrial genome. This revealed a novel point mutation (15967G>A) in the tRNA gene for proline which was heteroplasmic in muscle, present at lower levels in mitotic tissues and segregated with COX deficient fibres on single fibre PCR analysis. Moreover, the 15967G>A transition was not present in databases of control sequences, was predicted to alter a conserved base pair in tRNA structure and its absence in urine and blood from the patient's muscle and two sisters suggests that it had arisen de novo as a sporadic event. The association of this unique mtDNA mutation with such an array of neurological features provides further evidence that the phenotypic spectrum of mtDNA disease continues to evolve, and that comprehensive mtDNA analysis may be required to identify the underlying genetic defect.

040 POOR OBSERVER AGREEMENT AMONG NEURORADIOLOGISTS IN DISTINGUISHING BETWEEN PRIMARY INTRACEREBRAL HAEMORRHAGE AND HAEMORRHAGIC TRANSFORMATION OF INFARCTION: IMPLICATIONS FOR SECONDARY PREVENTION

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Background: CT remains the gold standard for diagnosing acute primary intracerebral haemorrhage (PICH), but inter-observer reliability in distinguishing haemorrhagic transformation of infarction (HTI) from PICH has not been studied, despite often differing clinical management.
Methods: All CT scans showing intracerebral haematoma from the first 4 years of the Oxford Vascular Study (a prospective population based study of all acute vascular events, including stroke), were independently reviewed and diagnosed as PICH or HTI by five neuroradiologists. Two neuroradiologists reviewed a subset of the films twice.
Results: Of 840 strokes, 71 cases were identified with intraparenchymal haematomas on CT. Intra-rater agreements for PICH versus HTI of two observers were excellent (kappa values 0.88 (0.68–1.00) and 0.93 (0.79–1.00)), but their inter-rater agreement was poor ($k=0.21$, 0.00–0.42). Overall inter-rater agreement for the five observers was moderate at best ($k=0.40$, 0.17–0.63). Disagreement over the radiological diagnosis occurred in approximately half of the cases surviving >30 days, and was relevant to decisions regarding secondary stroke prevention, particularly for those with a concurrent high risk of thromboembolic events.
Conclusion: Differentiation between HTI and PICH on CT scan in acute stroke has only modest reproducibility. This finding has implications for clinical practice, epidemiological studies and CT based clinical trials.

041 ANTI-MAG SYNDROME: CLINICAL, ELECTROPHYSIOLOGICAL AND SEROLOGICAL CORRELATES

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The neuropathy associated with anti-myelin associated glycoprotein (anti-MAG) antibodies is typically a distal, predominantly sensory, demyelinating neuropathy, often accompanied by unsteadiness and tremor. It occurs in association with an IgM paraprotein, most commonly a monoclonal gammopathy of undetermined significance. Current diagnostic tests to identify anti-MAG antibodies include complement fixation, immunohistochemistry, enzyme linked immunosorbent assay (ELISA) and western blotting. The availability of commercial anti-MAG ELISA tests means their use is increasing but the sensitivity and specificity of this test is unknown. We have audited 100 consecutive anti-MAG requests received by a regional laboratory, looking at clinical, electrophysiological and immuno-

logical characteristics. We identified clinical and electrophysiological predictors of seropositivity, and compared the sensitivity of ELISA and western blot analysis in these cases. Anti-MAG antibodies should only be sought where there is clear clinical indication to do so, and positive results from an ELISA should be confirmed with western blotting.

042 WEIGHT LOSS IN IDIOPATHIC INTRACRANIAL HYPERTENSION: CAN WE DO BETTER?

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The association between obesity and idiopathic intracranial hypertension (IIH) has been well documented, and weight loss is associated with a more favourable visual outcome but failure to lose weight is common. A weekly weight management clinic for IIH cases at the National Hospital for Neurology and Neurosurgery has been established since January 2004.

A retrospective review of this clinic was conducted during March 2006 and included patients referred between December 2004 and December 2005. The main aims of the review were to determine whether dietary intervention is effective in the management of IIH in those referred for weight management advice.

47 patients were referred of whom 31 attended the initial consultation. Only 13 patients attended their follow-up appointments, of whom 8 successfully lost weight. Emotional eating (disordered eating) was reported by all patients who did not lose weight; some reported that they had been under the care of eating disorder clinics (with a specialist obesity management dietician), psychologists or counselling in the past.

Conclusion: This clinic seems to be unsuccessful for those who report emotional eating as a sole contributing factor for weight gain or inability to lose weight successfully. The dietician is unable to be effective, despite using appropriate weight loss strategies with this group of patients.

043 PARIETAL LOBE DEFICITS ARE A FEATURE OF FRONTOTEMPORAL LOBAR DEGENERATION CAUSED BY A MUTATION IN THE PROGRANULIN GENE

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We describe the clinical, neuropsychological and radiological features of a British kindred (family DRC255) with a C31LfsX34 mutation in the progranulin gene, a recently discovered cause of familial frontotemporal lobar degeneration (FTLD). There are 10 affected individuals in three successive generations, presenting with a mean age of 57.8 years (54–67) and mean duration of disease of 6.1 years (2–11). All cases exhibited a clinical and radiological phenotype compatible with FTLD based on current consensus criteria. However, the cases illustrated here, as well as a review of previously described families with progranulin mutations, suggests a number of common features, including behavioural change, often dominated by apathy, language output impairment with either verbal adynamia or non-fluent aphasia, and involvement of the parietal lobes. This last feature is supported by radiological evidence of atrophy extending posteriorly into the parietal lobe and pathological evidence of parietal lobe involvement at post mortem. We propose that parietal features consisting of limb apraxia, dyscalculia, visuoperceptual and/or visuospatial impairment are a feature of progranulin associated FTLD that may help differentiate these cases clinically and radiologically from other causes of FTLD. Progranulin mutations may disrupt functional frontoparietal processing streams within the dorsal cerebral hemispheres.

044 A NOVEL PRESENILIN 1 DELETION (EXON 6 Δ166) ASSOCIATED WITH EARLY ONSET FAMILIAL ALZHEIMER'S DISEASE

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Mutations in the presenilin 1 (PS1) gene on chromosome 14q24.3 are the most common cause of autosomal dominant familial Alzheimer's disease (FAD). FAD in turn accounts for approximately 5% of AD cases. We report a novel PS1 deletion in a patient expressing a canonical AD phenotype. This contrasts with deletions reported at other sites on PS1 in which atypical clinical features, notably spastic paraparesis, are common.

The proband presented at 40 years of age with a 2 year history of progressive loss of episodic memory. Her main symptoms were of misplacing objects, forgetting names and repetitive questioning. Other features were early topographical difficulties and dyscalculia. Her mother had died at 46 years of age after suffering dementia with prominent memory loss.

Neuropsychometry revealed global deficits, most notably affecting verbal and visual recall and visuoperceptual abilities. Neurological examination was normal.

MRI brain imaging revealed generalised, symmetrical cerebral atrophy, most marked in the medial temporal lobes. Analysis of PS1 revealed a 466–468 CTT deletion at codon 166.

This case of early onset dementia with a ''typical'' AD phenotype contributes to the wide phenotypic spectrum associated with different mutations in the PS1 gene.

045 CONTROL OVER CONFLICT DURING MOVEMENT PREPARATION IN HEMISPATIAL NEGLECT

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Hemispatial neglect following right hemisphere stroke is often associated with a poor functional prognosis. We hypothesise that difficulty initiating leftward movements might contribute to neglect of left space. Here we use a task to investigate how patients deal with conflict between competing leftward and rightward motor programmes.

24 right hemisphere stroke patients (16 with neglect) and 14 age matched controls moved a joystick left or right in response to a central target arrow flanked vertically by incongruent (opposite direction) or congruent (same direction) arrows, or neutral flankers (squares). The incongruent condition is normally associated with greatest conflict.

Unlike controls, parietal neglect patients were paradoxically faster to move rightward in the incongruent condition (right target arrow flanked by leftward arrows), but they showed the expected response delay in the left incongruent condition. The second neglect group, with inferior frontal lesions, were disproportionately slowed bilaterally by incongruent flankers but were slower to move left in the neutral (most visually distracting) condition.

These data reveal two causes of leftward directional slowing in the neglect syndrome: parietal patients fail to inhibit rightward movements appropriately whereas frontal damage increases susceptibility to distraction during leftward movement planning. Both of these directional motor deficits may exacerbate symptoms of leftward neglect.

046 IS ABNORMAL VISUAL FIXATION A BIOMARKER FOR AMYOTROPHIC LATERAL SCLEROSIS?

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Background: Although typical pathology has been identified in the ocular motor nuclei of patients with motor neurone disease (MND), eye movement studies have yielded little in the way of abnormalities. Fixation, however, has not been formally examined in MND, and abnormalities found may correlate with brainstem dysfunction.

Objectives: To examine abnormalities of fixation in patients with MND with a view to creating a potential biomarker for disease.

Methods: Eye movements were recorded in 45 MND patients and 45 age-similar controls using an infrared Scalar limbus system. Geometric mean saccadic intrusion amplitudes (GMSIA) were calculated with and without a target. All patients were tested with the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised and a neuropsychological battery.

Results: GMSIA (target on) was significantly larger in the MND group compared with controls ($p=0.01$) and in classical amyotrophic lateral sclerosis (ALS) cases compared with other types of MND (pure lower motor neuron and upper motor neuron predominant syndromes) ($p=0.02$). GMSIA was found to correlate with verbal fluency but not with bulbar dysfunction.

Conclusions: Although evidence does not suggest that fixation is a marker for brainstem dysfunction, ocular fixation is abnormal in MND, in particular classical ALS, and may have a role in distinguishing ALS from other variants of MND.

047 EPISODIC CONFUSION: THE FIRST REPORTED CASE OF TYPE II CITRULLINAEMIA IN EUROPE

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Background: Citrullinaemia type II (CTLN2) is a recessively inherited metabolic disorder associated with defects in the SLC25A13 gene on chromosome 7. It is caused by a deficiency in the hepatic mitochondrial transporter citrin and presents in the third and fourth decade as hyperammonaemic encephalopathy, requiring hepatic transplantation. Reported cases to date have been almost exclusively in East Asia.
History: A 40-year-old man of Pakistani origin presented with 3 month history of episodic confusion. Elevated citrulline and arginine, with hyperammonaemia implicated CTLN2. Subsequent clinical deterioration was relentless, despite maximal medical treatment, with development of cerebral oedema and death within the next 4 weeks. Genetic analysis revealed a novel mutation in SLC25A13. Consanguinity was prevalent in the patient's family. Genetic analysis and phenotyping of family members is ongoing.
Discussion: This is the first case of CTLN2 reported in Europe, and is associated with the isolation of a novel mutation in the SLC25A13 gene in a patient ethnically and geographically distinct from CTLN2 described in the literature to date. Early recognition of this disorder is critical for timely liver transplantation, the only effective therapy to date.

048 COMPARATIVE RELIABILITY OF TOTAL INTRACRANIAL VOLUME ESTIMATION METHODS AND THE INFLUENCE OF ATROPHY IN A LONGITUDINAL SEMANTIC DEMENTIA COHORT

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Purpose: To directly compare the reliability of different total intracranial volume estimation methods and address whether such methods are influenced by brain atrophy in neurodegenerative conditions.
Materials and methods: We contrasted several manual approaches using T1 weighted, T2 weighted and proton density (PD) acquisitions with two automated methods (SPM5 and FreeSurfer) in a cohort of semantic dementia subjects (n = 11) that had been scanned longitudinally.
Results: The methods that were least susceptible to atrophy involved a novel mid-cranial sampling of either PD or T2 weighted images; of these, the PD method was both more accurate in terms of mean absolute percentage difference and more user friendly. Full cranial sampling of PD and T2 data was less reliable because of inconsistencies between scans at the base and vertex of the cranium. The T1 method consistently underestimated TIV as atrophy progressed; it was the least reproducible and most labour intensive of the manual methods. The fully automated FreeSurfer method overestimated TIV with progressive atrophy and, surprisingly, the FreeSurfer results were even worse after optimising the transformation. SPM5 was more susceptible to atrophy than the mid-cranial methods, although it performed better than FreeSurfer.
Conclusion: The mid-cranial sampling of PD images achieved the best combination of accuracy, reliability and user friendliness.

049 TESTING THE ''BROKEN ESCALATOR PHENOMENON'' ON PATIENTS WITH MIDLINE CEREBELLAR LESIONS

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The ''broken escalator phenomenon'' describes the unsteady sensation on walking onto a stationary escalator despite knowing that it will not move. This is due to an after effect (AE) of gait adaptation. We investigated cerebellar involvement in AE production.
Methods: Six patients with midline cerebellar lesions and 12 age matched controls stepped from a fixed platform onto a treadmill. The protocol consisted of 10 stationary trials (BEFORE), 15 moving (MOVING) and 10 stationary (AFTER) trials. Trunk displacement and angular velocity were measured at foot–treadmill contact. Gait velocity was measured before foot contact.
Results: AEs were noted in AFTER trial 1 as increases in gait velocity compared with baseline for both controls (18.8% increase) and patients (11.5% increase). Gait velocity increased beyond 2 SD of baseline in seven (58.3%) controls and in two (33%) patients. Combining gait velocity, trunk overshoot and angular velocity, 33% of patients and 67% of controls had an AE ($p<0.05$, $c^2 = 1.77$).
Conclusions: Cerebellar patients showed deficits in the generation of this gait AE, in particular a lack of gait velocity increase. As gait velocity is measured before foot–treadmill contact, the findings imply cerebellar involvement in feed forward control of gait adaptation.

050 AN IMPORTANT CAUSE OF MYELOPATHY

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Background: Spinal arteriovenous dural fistula is a rare cause of myelopathy. It can progress slowly or have a relapsing–remitting course. Back pain is common and sphincter disturbance can occur.
Case presentation: A 74-year-old male acutely deteriorated with tetraparesis, decreased muscle tone and urinary retention after initially presenting with mild proximal weakness, a 4 month history of back pain and a 48 h episode of marked leg weakness 2 months earlier. A cervical spine MRI revealed extensive high signal within the cervical cord. He further deteriorated with respiratory involvement. The diagnosis of arteriovenous dural fistula was raised because of the stepwise progression of his symptoms. He declined further investigation and later died. The diagnosis was confirmed at post mortem.
Conclusion: Arteriovenous dural fistula is an important cause of spinal cord ischaemia, and if identified and treated early it can have a good prognosis. This diagnosis should always be included in the differential diagnosis of any progressive (particularly stepwise) myelopathy.

051 TWO NEW MOLECULAR MARKERS OF LEWY BODIES IN PARKINSON DISEASE

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We have performed whole genome transcriptome analyses in cases of sporadic Parkinson disease.[1] Microarray data analysis revealed 570 highly deregulated genes. Among the group of upregulated genes, we investigated expression of DNAJB6 which codes for DnaJ (Hsp40) homologue, subfamily B, member 6 and NPTX2 encoding neuronal pentraxin II. DnaJB6 is a chaperone linked to protein degradation and folding. Neuronal pentraxin II is a secreted protein which is likely to play a role in the modification of cellular properties that underlie long term plasticity. Immunocytochemical ''back-mapping'' of both gene products to substantia nigra and frontal cortex tissue resulted in striking labelling of Lewy bodies. At high magnification, differences compared with alpha-synuclein immunostaining were apparent. Apart from neurons, significant expression of DnaJB6 protein was also observed in astrocytes, supporting the view that glia may be directly affected in Parkinson disease.[2 3] Our studies show that whole genome microarrays are powerful tools which fertilise neurohistological research. In situ back-mapping of all gene products showing altered expression in disease states will represent a major challenge in future. This will require additional brain banking initiatives.

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052 SPINOCEREBELLAR ATAXIA TYPE I MIMICKING STIFF MAN SYNDROME

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A 47-year-old male Fijian labourer suffered crush injuries at work. One month later he noted an unsteady gait and panic attacks. Examination revealed minimal dysarthria, mild upper limb ataxia, mild paraparesis but pronounced rigidity of abdominal, paraspinal and lower limb muscles. He exhibited a stiff, almost robotic gait. Cerebrospinal fluid analysis, including oligoclonal bands and initial 1.5 T MRI of the brain and spinal cord were normal. Somatosensory evoked potentials and central motor conduction times were delayed from the lower limbs. Electromyography intermittently showed continuous motor unit activity in the proximal limb and paraspinal muscles consistent with stiff man syndrome (SMS). Bloods, including vitamin E levels, HTLV and neuronal, glutamic acid decarboxylase and amphiphysin antibodies, were normal or negative. Genetic testing confirmed spinocerebellar ataxia (SCA) type 1. Serial 3 T MRI revealed progressive cerebellar and cervical cord atrophy. Spinocerebellar ataxia mimicking SMS was recently reported in SCA3. We believe this to be the first report of SCA1 associated with a stiff man phenotype. Both cases had a suggestive phenotype with supportive electrophysiology, but had genetically proven SCA and an absence of the typical antibodies for SMS.

053 SPINAL CORD STIMULATION FOR POST-AMPUTATION LIMB PAIN

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Objective: Spinal cord stimulation of the dorsal columns by high frequency electrical pulses has been used since the early 1970s for relief of chronic intractable pain following limb amputation. However, the procedure is now little used and little reported. We report our experience with all 12 patients managed to date in our unit using modern techniques and providing ongoing aftercare.
Methods: All patients had quadripolar plate electrodes inserted by laminectomy and connected to subcutaneously implanted stimulators. Stimulation parameters were optimised during subsequent clinic appointments.
Results: Worthwhile benefit of initial mean magnitude of 66.4% (<15.5% SD) over a median period of stimulation of 11 years was achieved in seven patients (waning in two patients after 2 and 19 years). Two patients were lost to follow-up having initially had benefit, two had no stimulation in the pain region and one had spontaneous pain relief. Continued successful stimulation often required alteration of stimulating electrode contacts and sometimes operative revision of electrode location. A wound cyst developed in one patient. Six technical failures were all remedied by revision procedures.
Conclusion: These findings in patients otherwise resistant to treatment indicate that the procedure merits continued use with further efforts to refine the technique and patient selection.

054 TASTE IS ABNORMAL IN PARKINSON DISEASE AND SUGGESTS CORTICAL SPREAD

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Background: Parkinson disease (PD) spares the first and second order taste neurons (solitary tract and nucleus; VPM, thalamus). Sienkiewicz-Jarosz *et al*[1] found normal taste threshold in PD. We wished to verify this and whether there was a correlation between any taste and smell defect.
Methods: Taste threshold was estimated from the tongue tip (fungiform papillae) with a Rion electrogustometer and olfaction by the University of Pennsylvania Smell Identification Test (UPSIT) in 75 patients and 74 controls. PD patients were in Hoehn and Yahr stages 1–3 and scored 27 or more on the Mini-Mental Status Examination.
Results: Patient taste thresholds were greater than controls by 6.9 dB (95% CI 3.9, 9.9; $p<0.001$), allowing for age, sex and smoking. 20/75 scored outside the 95% reference range. Taste threshold increased marginally with age in patients but not controls ($p=0.039$). PD-UPSIT score was severely impaired (PD mean 19.5 (range 4–35); control mean 33 (range 13–40); $p<0.001$). There was no correlation between taste and smell, adjusted for subject status, age and sex (partial correlation coefficient −0.056; $p=0.505$).
Conclusion: Taste threshold is significantly and independently impaired in PD in about 25% of patients. Age and smoking have minimal effect. The first taste structure to show Lewy pathology is the frontal operculum. Hence taste impairment may indicate disease that has advanced into the frontal lobes (Braak stage 5).

055 CEREBELLAR ABNORMALITIES ASSOCIATED WITH DEVELOPMENTAL STUTTERING

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Comparison of persistent (PDS) and recovered (RDS) developmental stutterers offers an opportunity to understand the mechanisms of plasticity, reorganisation or recovery of function. Functional imaging studies in people who stutter (PWS) indicate overactivity of the cerebellum. Furthermore, structural cerebellar abnormalities are common to a range of developmental disorders, such as autism and dyslexia.

Here we used high resolution structural and diffusion tensor MRI to examine cerebellar structure in developmental stuttering. We measured grey and white matter (GM and WM) volumes and fractional anisotropy (FA) in the cerebellum in PDS, RDS and control groups.

In the posterior lobe, GM was reduced by 10% in PWS compared with controls ($p=0.04$); this was due mainly to the RDS group. There were no significant differences in WM volumes among these groups. In the anterior lobe, FA values showed a different pattern of symmetry among the groups: the RDS group showed a strong left>right asymmetry, whereas the PDS group showed a right>left asymmetry. The RDS group also had reduced FA in the left middle and superior cerebellar peduncles compared with controls.

We conclude that the significant abnormalities in the cerebellum of the RDS group are related to their successful reorganisation of function for fluent speech.

056 SPINAL CORD DIFFUSION IMAGING AND SPECTROSCOPY TO ASSESS THE IMPACT OF ACUTE LESIONS IN MULTIPLE SCLEROSIS

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Introduction: Disability in multiple sclerosis (MS) often relates to spinal cord involvement, underlining the importance of applying new imaging techniques to this area in order to guide the management of patients with MS. Here we applied diffusion tensor imaging (DTI) and single voxel 1H-MR spectroscopy (MRS) to the cervical cord of MS patients with an acute lesion in that area.
Methods: 13 MS patients at the onset of a cord relapse with at least one lesion between C1 and C3, and 13 age and sex matched controls, were studied. Diffusion measures of the corticospinal tract, including voxel based connectivity, and metabolite concentrations were obtained.
Results: Patients showed lower N-acetyl-aspartate ($p<0.001$, Mann–Whitney), lower connectivity ($p=0.016$) and lower fractional anisotropy ($p=0.007$) than controls. In the patient groups there were significant correlations between: (i) the Expanded Disability Status Scale and inositol, choline, phosphocreatine–creatine and connectivity, (ii) time walked test and choline and (iii) 9-hole peg test and connectivity (all p values <0.05, Spearman's rho).
Conclusion: DTI and MRS of the cervical cord are feasible on a clinical scanner and provide measures that relate to disability associated with acute lesions. The most striking result is that connectivity of the corticospinal tract, which indicates the integrity of fibres, is lower in MS patients and correlates with disability.

057 P53 DEPENDENT NEURONAL CELL DEATH IN A DJ-1 DEFICIENT ZEBRAFISH MODEL OF PARKINSON DISEASE

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Mutations in DJ-1 lead to early onset Parkinson disease (PD). The aim of this study was to elucidate further the underlying mechanisms leading to neuronal cell death in DJ-1 deficiency in vivo and determine whether the observed cell loss could be prevented pharmacologically. Inactivation of DJ-1 in zebrafish, Danio rerio, resulted in loss of dopaminergic neurons after exposure to hydrogen peroxide and the proteasome inhibitor MG132. DJ-1 knockdown by itself already resulted in increased p53 and Bax expression levels prior to toxin exposure without marked neuronal cell death, suggesting sub-threshold activation of cell death pathways in DJ-1 deficiency. Proteasome inhibition led to a further increase in p53 and Bax expression with widespread neuronal cell death. Pharmacological p53 inhibition either before or during MG132 exposure in vivo prevented dopaminergic neuronal cell death in both cases. Simultaneous knockdown of DJ-1 and the negative p53 regulator mdm^2 led to dopaminergic neuronal cell death even without toxin exposure, further implicating involvement of p53 in DJ-1 deficiency mediated neuronal cell loss. Our study demonstrates the utility of zebrafish as a new animal model to study PD gene defects and suggests that modulation of downstream mechanisms, such as p53 inhibition, may be of therapeutic benefit.

058 A CORRELATION OF MAGNETISATION TRANSFER RATIO HISTOGRAM MEASURES WITH CLINICAL DISEASE SEVERITY IN INHERITED PRION DISEASE

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Inherited prion diseases (IPD) are progressive neurodegenerative disorders in which conventional magnetic resonance (MR) neuroimaging is often

unremarkable. We investigated global and regional cerebral MR magnetisation transfer ratios (MTRs) in IPD. 23 patients, recruited into the MRC PRION-1 Trial, underwent MTR and conventional MR imaging. For each patient, whole brain MTR histogram mean (AVMTR), peak height (PH), peak location and MTR at the 25th, 50th and 75th percentiles (MTR25%, MTR50%, MTR75%) were calculated together with mean MTR for bilateral caudate, putaminal and pulvinar regions of interest (ROI). A clinician's assessment of disease severity (GIC), Clinician's Dementia Rating (CDR), Alzheimer's Disease Assessment Scale (ADAS-COG), activities of daily living (ADL), Brief Psychiatric Rating Scale (BPRS), Mini-Mental Score Examination (MMSE) and Rankin scores were evaluated. Significant ($p<0.01$) bivariate Spearman rank correlations were found between AVMTR and Rankin ($p=0.008$), CDR ($p=0.002$) and ADAS-COG ($p=0.004$); PH and Rankin ($p=0.002$); MTR25% and Rankin ($p=0.001$), CDR ($p<0.001$), ADAS-COG ($p=0.008$) and GIC ($p=0.006$); and MTR50% and Rankin ($p=0.004$). Mean ROI MTRs did not correlate with clinical scores, and there were no pathological appearances on conventional MR imaging. Whole brain MTR histogram measures may provide valuable indices of IPD disease severity for future therapeutic trials.

059 DIFFUSION MAGNETIC RESONANCE HISTOGRAMS AS A SURROGATE MARKER OF CEREBRAL SMALL VESSEL DISEASE PROGRESSION

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Introduction: Cerebral small vessel disease (SVD) is the most common cause of vascular dementia. Interest in using MRI parameters as surrogate markers of disease to assess therapies is increasing. A cross sectional study found that fractional anisotropy (a diffusion tensor imaging parameter) and brain volume correlated well with executive dysfunction. The aim of this study was to determine if longitudinal changes were detectable in these parameters and whether they correlated with changes in cognition.
Methods: 35 patients with a lacunar stroke and leukoaraiosis were recruited for cognitive testing and MRI. Of these, 27 returned after a year for repeat testing. The change in T1 brain volume, FLAIR lesion load, fractional anisotropy (FA) and cognitive scores were determined over 1 year using paired tests. The association between the changes in MR parameters and cognitive scores was calculated.
Results: The FA parameter changed by 10.7% ($p=2.3\ 10^{-5}$) compared with brain volume and lesion load which did not show a significant change (−0.9%, $p=0.4$; 1.1%, $p=0.1$). No cognitive changes were found and no correlation was detected between changes in MRI parameters and cognition.
Conclusion: These findings are consistent with DTI being a sensitive parameter to monitor white matter damage in patients with SVD.

060 CEREBROSPINAL FLUID AND SERUM CYTOKINE PROFILE IN PATIENTS WITH IDIOPATHIC INTRACRANIAL HYPERTENSION

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Objective: To identify CSF and serum cytokine and chemokine profiles associated with idiopathic intracranial hypertension (IIH).
Method: Antibody arrays were used to detect the relative expression of 42 cytokines, chemokines and growth factors in the CSF and serum of six IIH patients and six controls. The signals were detected with a chemiluminescence imaging system and the spots in the membrane were semiquantified using Labworks software. The relative levels of cytokines were expressed as a percentage of the mean positive control value on each membrane.
Results: In both patients and controls, multiple cytokines were detected, most being present at relatively low levels. Monocyte chemotactic protein (MCP)-1, MCP-2, MCP-3, macrophage inflammatory peptide (MIP)-1d, monocyte induced by gamma interferon (MIG), RANTES, interleukin (IL)-1a, leptin and IL-8 were more highly expressed. MCP-1 was increased in CSF, and MCP-2, MCP-3, MIP-1d, IL-1a and leptin in serum were significantly higher in IIH patients compared with controls.
Conclusion: This is the first report demonstrating differences in cytokine expression in the serum and CSF in IIH patients compared with controls. As the aetiology and pathogenesis of IIH are still unclear, the heterogeneity of the observed cytokine expression reported here may be of significance.

061 TRANSIENT MRI ABNORMALITY IN A PATIENT WITH NON-KETOTIC HYPERGLYCAEMIA AND EPILEPSIA PARTIALIS CONTINUA

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A 54-year-old man presented with epilepsia partialis continua (EPC). He had raised blood glucose with high osmolality. CT brain, CSF and C reactive protein were normal. Blood sugar fluctuated between 20 and 30 mmol/l. EEG showed continuous focal seizures and MRI scan showed a localised high signal lesion in the left cingulated gyrus with mass effect suspicious of a neoplastic lesion.

Seizures did not respond to phenytoin but resolved completely after normalisation of blood glucose. There was no residual focal neurology. MRI scan was repeated for further evaluation of the lesion but the abnormality had completely resolved.

Focal seizures are a recognised complication of non-ketotic hyperglycaemia (NKH) but it is rare to present with EPC. MRI abnormalities had been described in NKH and they are attributed to associated vascular events. The disappearance of MRI changes has not been reported in the literature. EPC and MRI changes are likely to be due to metabolic changes of NKH rather than ischaemia. Poor response to antiepileptic medications, rapid recovery following correction of NKH and normalisation of the MRI support the metabolic theory.

NKH should be considered in patients presenting with EPC, as it may be the first ever presentation of diabetes.

062 USE OF SKIN BIOPSY AND CONTACT HEAT EVOKED POTENTIALS TO IDENTIFY POSSIBLE SMALL FIBRE VARIANTS OF INFLAMMATORY NEUROPATHY AND GUILLAIN–BARRE SYNDROME

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Counts in intraepidermal fibres (IEF) of the nerve markers protein gene product (PGP) and the heat and capsaicin receptor TRPV1, and the contact heat evoked potential stimulator (CHEPS), are useful for the diagnosis of small fibre peripheral neuropathy.

In a study of patients presenting with symptoms of small fibre neuropathy (SFN), we identified a subgroup of 10 patients with symptoms of hypersensitivity, usually of rapid onset. Patients within the hypersensitive subgroup had preserved PGP and TRPV1 IEF counts, unlike patients with a more classical presentation of small fibre neuropathy (mean (SEM) values; control: PGP 6.5 (1.4), n=6, TRPV1 5.7 (1.4), n=9; hypersensitive: PGP 3.9 (0.8), n=10, TRPV1 7.6 (0.9), n=10; non-hypersensitive SFN: PGP 2.3 (0.4), n=22, TRPV1 1.3 (0.3), n=22) and preserved TRPV1/PGP IEF ratio (control 0.88, n=6; hypersensitive 1.96, n=10; SFN 0.57, n=22). However, in common with patients with SFN, they had significantly reduced epidermal thickness (mean (SEM) μm; control: 100.1 (1.4), n=12; hypersensitive: 74.8 (5.7), n=10, $p=0.0496$; SFN: 73.3 (3.9), n=22, $p=0.0258$) and a reduced CHEPS amplitude from the leg (mean (SEM) μV; control: 11.5 (1.7), n=7; hypersensitive: 3.3 (1.4), n=10, $p=0.0392$; SFN: 2.0 (0.9), n=22, $p=0.0002$), in keeping with a diagnosis of neuropathy.

We postulate that these hypersensitive patients may present with a proximal inflammatory neuropathy predominantly affecting small fibres, as inflammation upregulates TRPV1 expression.

063 LOCALISED GREY MATTER MAGNETISATION TRANSFER RATIO CHANGES CONTRIBUTE TO DISABILITY IN PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

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Background: MRI techniques have demonstrated considerable damage to the normal appearing grey matter in primary progressive multiple sclerosis (PPMS), including reduced magnetisation transfer ratio (MTR) and volume loss. In this study, we localised the damaged areas, compared the two parameters and investigated the clinical impact of the MTR changes.
Methods: 46 patients with PPMS and 23 controls underwent MT and high resolution T1 weighted imaging. The Expanded Disability Status Scale (EDSS) was scored. Grey matter volume and MTR were compared between patients and controls on a voxel-by-voxel basis. MTR for regions within the motor network were correlated with EDSS, adjusting for age and grey matter volume.
Results: Patients showed reduced MTR and atrophy in the right pre- and left post-central gyri, right middle frontal gyrus, left insula and thalamus bilaterally. Reduced MTR without atrophy occurred in the left pre- and post-

central gyri, left superior and inferior frontal gyri, superior and middle temporal gyri, and visual cortex. Higher EDSS correlated with lower MTR in the primary motor cortex bilaterally ($p<0.05$).
Conclusion: Localised grey matter damage occurs in PPMS, and regions of MTR reduction are more widespread than areas of irreversible volume loss. Damage demonstrated by MTR and volume changes is clinically eloquent.

064 PARANEOPLASTIC SENSORIMOTOR NEUROPATHY ASSOCIATED WITH REGRESSION OF PRIMARY SMALL CELL LUNG CANCER

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Background: Paraneoplastic sensorimotor neuropathies have been commonly associated with small cell lung carcinoma, particularly in the presence of anti-Hu antibodies.
Case report: A 70-year-old female smoker presented with nausea, anorexia and weight loss. Chest *x* ray revealed a right hilar mass; CT chest confirmed a lobulated mass in the right middle lobe with subcarinal and hilar lymphadenopathy. A diagnosis of small cell lung carcinoma was made when washings and biopsies revealed a few atypical cells, suggestive of a small cell neoplasia. She subsequently developed a progressive sensorimotor neuropathy with high titres of anti-Hu antibodies in her serum. The clinical manifestations of the neuropathy were temporally associated with marked regression in the lung neoplasm, with no evidence of neoplasia on radio imaging (CT and positron emission tomography) or bronchoscopy within weeks of presenting with the neuropathy. Eighteen months after her initial diagnosis she remains clinically stable.
Discussion: Previous case series suggest that anti-Hu antibodies may be associated with less extensive disease, prolonged survival and increased chemosensitivity. However, tumour regression associated with anti-Hu antibodies has only been reported in four other cases worldwide. We feel this case supports the theory that anti-Hu antibodies, produced as a paraneoplastic phenomenon of small cell lung carcinoma, confer antitumour activity causing tumour regression.

065 TWO SPORADIC CASES OF RAPID ONSET DYSTONIA PARKINSONISM

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Rapid onset dystonia parkinsonism (RDP) is a rare genetic movement disorder recognised by sudden onset of bulbar and limb dystonia with parkinsonism; neuropsychiatric features are common. We report two unrelated cases.

Case 1, a 20-year-old man, admitted with subacute onset of dystonia in the upper and then the lower limbs, and facial and bulbar muscles with generalised rigidity and slowing. Maximal disability was reached within 7 days. He remains mute and wheelchair bound at 4 years after his initial symptoms. Case 2 is an almost identical presentation in a 20-year-old woman whose pyramidal and extrapyramidal signs were preceded by 2 weeks of emotional lability. Neither was dopamine responsive.

Both cases have a confirmed point mutation in ATP1A3 gene on chromosome 19q3. This gene has been shown to code for an integral protein in the neuronal membrane Na+/K+-ATPase pump. The inheritance is usually autosomal dominant with incomplete penetrance. We present two sporadic cases highlighting the importance of considering this diagnosis and screening for the gene despite the absence of a family history. We have video evidence to demonstrate this.

066 CONNEXIN 32 MUTATION PRESENTING WITH MONOMELIC MULTIFOCAL MOTOR NEUROPATHY WITH CONDUCTION BLOCK

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X-linked Charcot–Marie–Tooth disease (CMT), secondary to connexin 32 mutations, presents with generalised sensorimotor neuropathy. Although females can be asymptomatic, there are always abnormalities on physical examination and/or neurophysiology (NCS).

A 42-year-old woman first presented in 1996 with a 5 year history of wasting and weakness of the left hand. Examination revealed wasting and weakness in the forearm flexors and extensors and the small muscles of the hand. Sensation was normal. NCS revealed conduction block and a normal sensory action potential in the left median nerve, suggesting multifocal motor neuropathy with conduction block (MMN).

She underwent three trials of intravenous immunoglobulin (1997, 2004, 2006) and a trial of azathioprine (1997–1998) without clinical response. Her power continues to decline but only in the left arm. Repeated NCSs remain normal in all other limbs.

She has a novel heterozygous mutation of the connexin 32 gene—Asn226Ser. To date, all amino acid changing mutations in connexin 32 have been pathogenic.

This case suggests that either MMN can rarely be associated with connexin 32 mutations or, alternatively, if the MMN is a coincidental disease, this represents the first non-pathogenic mutation in connexin 32. Further functional studies are planned to resolve this issue.

067 LIFE ON MARS: LIVING WITH KLEINE–LEVIN SYNDROME

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Kleine–Levin syndrome (KLS) is a rare condition characterised by periods of hypersomnolence that may be associated with hyperphagia, hypersexuality and behavioural symptoms. A cause for the condition is unknown; hypothalamic disturbance has been postulated. It has been suggested that KLS exists in primary and secondary forms: the primary form that is not associated with a brain disorder is more common. It typically affects adolescent males and resolves spontaneously by their late twenties. Sufferers of secondary KLS are older and tend to experience more prolonged episodes of sleep disturbance. In both forms, episodes of hypersomnolence may be heralded by infection. There is no definitive treatment for the condition.

We report a man in his fifties who experienced hypersomnolence associated with vivid dream re-enactment and behavioural disturbance. Each episode followed a mild herpes simplex infection. During these episodes, which he recalled after the event, he had the experience of going into space to repair the space shuttle. He had no abnormality on neurological examination, lumbar puncture, EEG or structural MRI. The case highlights problems with the diagnosis of this disorder that might present to psychiatrists or neurologists in the absence of any definitive tests.

068 A PHASE III DOUBLE BLIND, RANDOMISED, PLACEBO CONTROLLED STUDY OF THE EFFICACY, SAFETY AND TOLERABILITY OF IDEBENONE IN THE TREATMENT OF FRIEDREICH'S ATAXIA PATIENTS

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UK Investigators: N Wood, R Surtees, W McKenna, London, UK, and P Chinnery, Newcastle, UK

Rationale: Idebenone is a short chain benzoquinone derivative which has positive effects on mitochondrial bioenergetics as well as antioxidant properties, mechanisms which may be relevant to the treatment of Friedreich's ataxia (FRDA). Positive effects of idebenone have been reported on the cardiomyopathy associated with FRDA, although older studies on its effect on neurological function have yielded conflicting results. A recent study at the NIH indicated positive effects of higher doses of idebenone on neurological function, suggesting that adequate dosing may be needed to observe effects in the central nervous system.

The study aims to confirm the positive effect on neurological function, assessed using the International Cooperative Ataxia Rating Scale and the Friedreich's Ataxia Rating Scale. Effects on cardiac mass and function will also be assessed using MRI and detailed echocardiography, including strain rate imaging. Safety and tolerability will be carefully monitored. The study plans to enrol approximately 204 patients in sites around Europe.
Dosage: Patients are randomised in a 1:1:1:1 ratio to blinded administration of one of three treatment arms of oral idebenone (low, medium or high dose), or placebo.

069 SAMPLE SIZE CALCULATIONS FOR EVALUATING NEUROLOGICAL RATING SCALES: HOW MANY IS ENOUGH?

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Sample size calculations in neurological research are essential to ensure that studies are adequately powered. However, sample size calculations are not applicable to rating scale evaluations. Therefore, this study examined the empirical impact of different sample sizes on the stability and

interpretation of core reliability and validity estimates, with the view to propose guidelines.

We undertook two studies. In study 1, data were analysed retrospectively from 713 people with multiple sclerosis (MS) who had completed the MS Impact Scale. We reduced the total sample randomly and non-randomly. In study 2, a prospective analysis was carried out on data from 391 people with cervical dystonia (CD) who had completed the CD Impact Profile. In both studies, core indicators of reliability and validity were undertaken.

Reliability estimates remained constant and fulfilled the criteria in all subsamples in studies 1 and 2, including the smallest subsample ($n = 20$). Validity scores were not as stable in the smaller samples ($n < 40$), although in general above this number of subjects, recommended criteria were reached and hypothesis testing reflected the largest sample scores.

In these studies, low sample sizes ($n > 20$ for reliability and $n > 80$ for validity analyses) can provide useful indicators of core psychometric properties.

070 A CASE OF CONGENITAL BILATERAL PERISYLVIAN SYNDROME (WORSTER–DROUGHT) DIAGNOSED IN ADULTHOOD

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A 30-year-old man presented to the neurology service for the first time with generalised convulsions. He had suffered convulsions between the ages of 5 and 7 years which had never been investigated or treated. There was also a history of learning difficulties. He had undergone oral surgery as an infant for a ''tongue problem'' but it had been unsuccessful. On examination, he was noted to dribble, have a marked dysarthria and was unable to protrude his tongue. On EEG there were some suspicious right temporal spikes. CT showed cerebral atrophy. Despite treatment he continued to have seizures, requiring high doses of anticonvulsants. MRI showed extensive polymicrogyria affecting the insular lobe, posterior frontal and anterior parietal lobes. The history of a congenital suprabulbar paresis, learning difficulties and epilepsy with insular polymicrogyria on the MRI brain suggested a diagnosis of congenital Perisylvian syndrome (Worster–Drought syndrome).

071 PSEUDOENHANCEMENT OF MULTIPLE SCLEROSIS MRI LESIONS AFTER IV IRON THERAPY

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Cranial MRI is used in the diagnosis of multiple sclerosis (MS) in accordance with the McDonald criteria. The presence of gadolinium enhancing lesions indicates recent breakdown of the blood–brain barrier and is also used in research studies to monitor disease activity. In clinical practice, MRI may guide treatment decisions.

We report the case of a 44-year-old female patient with relapsing–remitting MS who was treated with the monoclonal antibody alemtuzumab (Mab-Campath) in February 2005. She had a cranial MRI scan prior to further treatment in 2006 which showed a rim of hyperintensity around several periventricular lesions on pre-contrast axial T1 images, identical to the post-contrast scan. She had received intravenous iron sucrose (Venafer) for anaemia several months previously. We postulate that at the time of infusion she had active MS leading to brain iron deposition in new areas of demyelination.

Superparamagnetic iron oxide nanoparticles have been developed as a novel MRI contrast agent and are taken up in inflammatory reticuloendothelial cells. Therapeutic intravenous iron may also lead to significant brain iron deposition in MS patients leading to ''pseudoenhancement'' on MRI which may be misinterpreted as fresh disease activity unless clinicians are aware of this phenomenon.

072 SEVERE CHARCOT–MARIE–TOOTH TYPE I NEUROPATHY DUE TO CO-OCCURRENCE OF A PERIPHERAL MYELIN PROTEIN-22 DUPLICATION AND A NOVEL MYELIN PROTEIN ZERO MUTATION

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Objective: To describe the first family with both peripheral myelin protein 22 (PMP-22) duplication and a novel myelin protein zero (MPZ) mutation.

Background: Charcot–Marie–Tooth disease (CMT) is a clinically and genetically heterogeneous inherited neuropathy. PMP-22 duplication and MPZ mutations cause dominantly inherited demyelinating neuropathies. MPZ mutations have also been linked with additional signs, including pupillary abnormalities as well as inherited axonal neuropathy.

Results: Two siblings demonstrated a severe progressive sensorimotor neuropathy with distal weakness and atrophy with onset in childhood. Both had abnormal pupillary responses with the elder's pupillography showing small pupils with near-light dissociation and supersensitivity to pilocarpine with no reaction to cocaine, indicating a neurological origin. No other autonomic dysfunction was demonstrable. Motor nerve conduction velocities were slowed and sensory responses from all limbs were absent. Both had PMP-22 duplications and a novel MPZ missense mutation in exon 2.

Conclusions: The coexistence of pathogenic mutations in two different CMT genes appears to result in the severity of the neuropathy seen. Families with CMT1 with additional clinical abnormalities, including abnormal pupillary responses, should be evaluated for MPZ mutations regardless of PMP-22 status as the coexistence of two different mutations may lead to a more severe neuropathy which is prognostically important.

073 ERYTHROPOIETIC PORPHYRIA DOES CAUSE NEUROLOGICAL DISEASE

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Background: Acute intermittent, variegate copro-porphyria are renowned for causing neurological manifestations. Erythropoietic protoporphyria (EPP) presents with photosensitivity and hepatic dysfunction but an associated progressive neurological disturbance has never been described. Here we present a family with EPP in which the proband presented with spastic paraparesis. We also describe another five families with true recessive inheritance, which occurs in only 3% of cases of EPP.

Patients and methods: The 55-year-old proband was the product of a consanguineous marriage. Photosensitive rash with keratoderma occurred when aged 1 year. Diagnosis of EPP was made at age 30 years. Subsequently he noticed that he was dragging his legs and was tripping. Examination revealed spastic paraparesis with absent ankle jerks. His older sister described similar skin problems but no neurological sequelae.

Results: Urine porphobilinogen and aminolevulinic acid levels were normal with elevated erythrocyte total porphyrin. DNA sequencing of the ferrochelatase gene showed that the proband was homozygous for the 416 t>a mutation (Q139L). MRI scan of the head showed white matter changes consistent with leucodystrophy with predominant periventricular distribution, sparing the anterior limb of the internal capsule bilaterally. Nerve conduction studies showed an axonal neuropathy.

Conclusions: EPP does cause neurological disease. The presence of palmar keratoderma, preserved liver function and lower levels of blood porphyrins may predict neurological manifestations in EPP. These manifestations may be acute or chronically progressive. In a patient presenting with spastic paraparesis and leucodystrophy sparing the anterior limb of the internal capsule, EPP should be considered.

074 BILATERAL CORTICO-STRIATE GREY MATTER CHANGES SUPPORT THE SENSORY ENDOPHENOTYPE HYPOTHESIS IN FAMILIAL ADULT ONSET DYSTONIA: A VOXEL BASED MORPHOMETRY STUDY

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Background: Regional volumetric grey matter changes and loss of normal neural somatotopy have been described in patients with adult onset primary torsion dystonia (AOPTD). Abnormal spatial discrimination thresholds (SDTs) are found in AOPTD and as an endophenotypic trait in unaffected relatives.

Objective: We hypothesise that unaffected relatives of AOPTD patients with abnormal SDTs also have morphological grey matter changes in the striato-pallido-thalamo-cortical circuit compared with unaffected relatives with normal SDTs.

Methods: Voxel based morphometry (VBM) was used to analyse high resolution T1 weighted MRI images. From 5 multiplex AOPTD families, 14 unaffected relatives with abnormal SDTs, 14 age, sex and family matched relatives with normal SDTs and 14 healthy control subjects were recruited.

Results: Bilateral reduction in grey matter volume (GMV) was found in the body of the caudate nucleus in the 14 relatives with abnormal SDTs compared with those with normal SDTs. All 28 unaffected family members had a bilateral increase in GMV in the post-central gyrus relative to controls. These findings remained significant after false detection rate correction at 0.05.
Conclusion: This study describes a new structural endophenotype in AOPTD and supports the proposed SDT abnormality as a marker of genetic susceptibility to the disease.

075 A NOVEL PATHOGENIC MUTATION OF THE TRANSTHYRETIN GENE

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We report a 74-year-old Irish female with a 2 year history of upper and lower limb weakness and paraesthesia, and a past history of bilateral carpal tunnel syndrome (CTS). Examination was consistent with a moderate, predominantly sensory, peripheral neuropathy. Several family members had similar complaints, including CTS, peripheral neuropathy and cardiac problems.

Nerve conduction studies identified a large fibre sensorimotor neuropathy. Autonomic function tests revealed mild cardiovascular autonomic dysfunction. A serum amyloid protein scan was negative, but echocardiography suggested cardiac amyloid. DNA analysis of two affected family members and our patient was negative for the common Irish mutation (TTRAla60) in the transthyretin gene (TTR) but revealed a novel His110Asp mutation. Amyloid deposits were identified within the sural nerve of our patient confirming the mutation to be pathogenic.

This case illustrates a novel pathogenic mutation in the transthyretin gene. Further study of its phenotype and penetrance will allow accurate counselling, predictive testing and decisions about appropriate treatments.

076 DIFFUSION TENSOR IMAGING DEFINES SUBREGIONS OF HUMAN LATERAL PREMOTOR CORTEX WITH DISTINCT FRONTOPARIETAL CONNECTIONS

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The lateral premotor cortex (LPMC) is implicated in motor recovery but its study as a single entity may be too crude an anatomical partition because of its diverse functions.

Functions of the dorsal LPMC (PMd) include visuospatial motor control and arbitrary stimulus–response mapping, whereas the ventral LPMC (PMv) is involved in object based visuomotor control and grasping. In macaques, the anatomical connectivity of these distinct subregions reflects their functional specialisations. We tested the relationship between functional and anatomical organisation in human LPMC using diffusion tensor imaging (DTI).

DTI data were obtained in 17 healthy controls. Using a method designed to search for differences in anatomical connectivity, we defined two distinct regions within the LPMC. These two regions, putative human PMd and PMv, had distinct patterns of frontoparietal connectivity. The PMd/PMv border defined using anatomical connectivity was close to a border defined using activations from previous functional MRI studies.

This approach can be used to identify in vivo PMd and PMv in the human brain. Future studies of the role of LPMC in motor recovery should differentiate PMd and PMv. They have distinct anatomical connectivity and functional pathways and may therefore have distinct roles in functional recovery.

077 SUBACUTE INFLAMMATORY DEMYELINATING POLYNEUROPATHY FOLLOWING PRIMARY VARICELLA ZOSTER VIRUS INFECTION

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There are many neurological complications of both primary and secondary infections with varicella zoster virus (VZV), including acute inflammatory demyelinating polyneuropathy. However, the more chronic variants of this condition, such as subacute inflammatory demyelinating polyneuropathy (SIDP) and chronic inflammatory demyelinating polyneuropathy, have not been reported to date.

We present the case of a 65-year-old man who developed severe left leg weakness, accompanied by mild weakness in the right hip flexion and the small hand muscles, 2–3 weeks following primary VZV infection. The first manifestation was severe neuropathic pain in the left leg followed by weakness, evolving over the course of 2 months. He had a past history of lymphoma and, over the preceding year, had received numerous chemotherapy agents and undergone bone marrow transplantation. Nerve conduction studies revealed a patchy demyelinating polyneuropathy. Imaging of the neuroaxis was unremarkable. CSF analysis in the acute phase demonstrated a high protein level (1.8 g/l). No evidence of lymphoma recurrence was identified. Sural nerve biopsy showed axonal loss with evidence of an inflammatory infiltrate.

He was bed bound for approximately 8 weeks, by which time his symptoms started to resolve spontaneously, supporting the working diagnosis of SIDP. This case illustrates a novel immunological consequence of primary VZV infection.

078 JARGON LANGUAGE IN FRONTOTEMPORAL LOBAR DEGENERATION

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We describe two patients with a clinical diagnosis of frontotemporal lobar degeneration who produced jargon as part of their language impairment (either in speech—jargon aphasia—or writing—jargon agraphia). Jargon is the production of incomprehensible language, normally secondary to neurological disease, and three types have been described: semantic, phonemic and neologistic jargon. Patients may have one or more of these types of jargon present as part of the same disorder. Jargon most commonly occurs after an acute neurological event, in particular Wernicke's aphasia, and is rarely described in neurodegenerative disease. One of the described cases had a diagnosis of semantic dementia and produced semantic and neologistic jargon. The other case had a diagnosis of progressive non-fluent aphasia and produced both phonemic and neologistic jargon. We describe the clinical, neuropsychological and radiological features of these cases and then go on to discuss the neuroanatomical correlates of the production of jargon and why it is such a rare occurrence in degenerative disease.

079 PREDICTIVE FACTORS FOR SURVIVAL IN MULTIPLE SCLEROSIS: A 21 YEAR PROSPECTIVE POPULATION BASED ANALYSIS

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Objective: To analyse predictive factors for death in a population based cohort of patients with multiple sclerosis over 21 years of follow-up.
Method: A prevalence study in South Wales in 1985 identified 441 patients (117/100 000), 86% of whom had definite or probable MS by Poser criteria and 14% had suspected MS. 301 patients were examined and Expanded Disability Status Scale (EDSS) determined together with functional scores and demographic details. Death certificates have been collected prospectively from this cohort and prognostic factors for survival determined.
Results: 379 patients were included in the analysis; 62 were excluded of whom 46 had suspected disease in 1985 with no further events or reinvestigation, and 16 in whom the diagnosis had been reviewed. 222 (58.6%) patients had died, 147 (38.8) were alive and current status was unknown in 10 (2.6%). Mean survival was 37.63 years (95% CI 35.92 to 39.34). Multivariate analysis showed that older age at onset ($p<0.0001$) and the presence of ataxia ($p=0.01$) were associated with shorter survival. Predictive value of factors from prevalence day in 1985 were also assessed. Higher sensory functional systems scores ($p=0.01$), number of functional system scores grade 5 or 6 ($p=0.03$) and longer disease duration ($p<0.001$) were all associated with shorter survival.

080 FALLING ON YOUR FACE: TRAUMATIC ANTERIOR REPEATED DENTAL INJURIES WITH SEIZURES ARE SPECIFIC FOR JUVENILE MYOCLONIC EPILEPSY

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Background: Patients can sustain injuries during seizures and the pattern and type of injury, for example tongue biting, can be a useful silent witness

in the diagnosis of seizures. In addition, the seizure type potentially influences the type of injury.
Methods: Patients with facial and dental injury were identified from the Gloucestershire Epilepsy Database (n = 1673). These patients' notes were reviewed and the following data collected: demographic data; seizure types and age of onset; injury; EEG; and MRI.
Results: The 14 people with dental injuries were: 10 incisors (9 had >1 incisor) and 5 other teeth. 8 patients had juvenile myoclonic epilepsy (JME), 2 had other primary generalised epilepsies, 3 had focal onset epilepsy and 1 was unclassified. Compared with the rest of the database population (JME; n = 81) there was a highly significant association of dental injury with JME ($p<0.01$) which was highly specific for multiple incisor injury (99.8%).
Conclusions: Bilateral incisor injury is rare but appears to be specific for JME in patients with epilepsy, presumably reflecting the pattern of seizure onset. This pattern of injury should prompt consideration of this diagnosis. It is hoped that recognition of this can both facilitate earlier diagnosis and help educate patients to protect their teeth.

081 ACUTE STROKE MANAGEMENT IN A DISTRICT GENERAL HOSPITAL

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Background: Acute stroke units (ASU) and thrombolysis improve outcome for stroke patients. We sought to document delays in hospital admissions, failures in accessing an ASU and the clinical impact of missed opportunities in stroke patients.
Methods: Delays, demographic details, risk factors and stroke features were recorded prospectively in all stroke patients admitted to a district general hospital (DGH) for 12 months. Using established numbers needed to treat to prevent disability or death, the clinical impact of the lost opportunities was determined.
Results: Of 171 acute stroke patients, 118 (69%) spent some of their hospital stay in an ASU. Less severe strokes, living alone and attending a general practitioner all independently delayed hospital admission. 19 (12.5%) ischaemic stroke patients would have been eligible for thrombolysis. Failure to admit all patients to the ASU cost two patients their independence, prevented two patients from living at home and resulted in one death. Failure to thrombolyse eligible acute ischaemic stroke patients resulted in six patients having more disability, two of whom may have lost their independence.
Conclusions: Improved access to an ASU is required in this DGH. Thrombolysis is feasible, but subregional stroke centres in selected district general hospitals with appropriate inter-hospital coordination may improve stroke care.

082 SECONDARY PREVENTION FOLLOWING CERVICAL ARTERY DISSECTION: A META-ANALYSIS

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Cervical artery dissection (CAD) is the commonest cause of stroke in young patients less than 55 years of age. To decide the practicability of a randomised trial, we performed a preliminary meta-analysis.
Method: A systematic review was performed using Cochrane guidelines. We searched Medline and Pubmed (1966 to August 2006) for prospective and retrospective studies which used both antiplatelets and anticoagulants in the treatment of CAD, and hand searched reference lists. We used Review Manager version 4.2. Outcome events (transient ischaemic attack (TIA), stroke, death) were identified in each treatment group. Studies of >4 patients were included.
Results: From a total of 2857 citations, we identified 33 studies (632 patients). No randomised controlled trials were identified comparing antiplatelets with anticoagulants. In total there were 11 deaths and 9 strokes. The risk difference comparing antiplatelets with anticoagulants was non-significant for death (95% CI 2% (−3% to 8%) (NS), stroke (1% (−5% to 6%) (NS) and TIA (95% CI 6% (0% to 12%) (NS).
Conclusion: There are few data from high quality studies to decide whether antiplatelet agents or anticoagulation provide more effective secondary prevention in CAD. No previous randomised trials have been performed because of the theoretically large number of patients required, yet they are essential to answer this question.

083 AMYGDALA FUNCTIONAL MRI IN MESIAL TEMPORAL LOBE EPILEPSY?

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Purpose: Anterior temporal lobe resections (ATLR) benefit up to 70% of patients with intractable temporal lobe epilepsy (TLE), but may be complicated by emotional disturbances. The aim of this study was to use functional MRI (fMRI) to investigate the role of the amygdala in processing emotion in TLE patients. It also may have the potential to be a preoperative predictive marker for emotional disturbances following surgery.
Methods: We studied 27 patients with intractable unilateral mesial TLE (mTLE: 16 with left hippocampal sclerosis, 11 with right hippocampal sclerosis) undergoing presurgical evaluation, and 14 healthy controls, using a fearful face fMRI paradigm. To investigate the state of anxiety and depression, the Hospital Anxiety and Depression Scale was used.
Results: Both patients and controls demonstrated bilateral amygdala activation on viewing fearful faces, greater on the right. Controls had greater activation in both the right and left amygdala compared with left and right TLE patients. There was a significant correlation between right amygdala activation and anxiety score in left TLE patients.
Conclusion: The fearful face paradigm is a reliable and reproducible method for measuring amygdala activation in controls and patients with mTLE. Postoperative follow-up will determine whether preoperative fMRI is a useful predictor of mood disturbances following ATLR.

084 SEIZURES ON ''YOU TUBE'': HOW IS EPILEPSY REPRESENTED IN THE NEW MEDIA

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There is a long history of epilepsy being represented in the media, from medieval tableaux to movies throughout the past century. With the explosion of internet entertainment, we wished to see how epilepsy was portrayed on ''You Tube'', one of the largest video sharing sites on the web, containing over 70 000 000 videos with 40 million registered users, most in western Europe and the US. Searching using the terms ''epilepsy'' and ''seizure'' produced a total of 1169 separate videos under several genre headings which are chosen by those who upload the video. Most were classified as either comedy (30%), people (24%) or entertainment (23%). Review of the videos reveals substantial amounts of educational material but also a high percentage of pseudoseizures, ''epilepsy self tests'', home videos of genuine seizures and jokes at the expense of those with epilepsy. Pseudoseizures outnumbered genuine epileptic events by over 10:1. Encouragingly, comments from other users about videos portraying pseudoseizures or exploiting those having genuine attacks were mostly condemning, with few exceptions. The spectrum of representation of seizures is much broader on ''You Tube'' than in traditional media although the high proportion of pseudoseizures and ''comedy'' videos suggests stereotypes and negative perceptions of epilepsy persist in new media.

085 VASCULAR LESIONS UNDERLYING ADULT PRIMARY INTRACEREBRAL HAEMORRHAGE

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Introduction: We investigated the yield of cerebral angiography (CA) in patients with primary intracerebral haemorrhage (PICH) in two settings: patients referred regionally for CA and patients presenting to a district stroke unit.
Methods: PICH patients were identified retrospectively from October 2003 to October 2006. Data on patient age, sex, hypertension, bleed location and imaging findings were recorded.
Results: In the stroke unit group (n = 75), four patients had CA yielding one arteriovenous malformation (AVM) and one mycotic aneurysm. 43 bleeds were attributed to hypertension, 10 to warfarin and 7 to amyloid angiopathy. In the regional group (n = 81), all had CA yielding 32 AVMs and 2 developmental venous anomalies. Overall, factors associated with high angiographic yield were age ⩽46 years (56%, $p = 0.028$) and normal blood pressure (53%, $p = 0.029$). The highest yield was recorded in primary intraventricular haemorrhage (71%) followed by lobar supratentorial haemorrhage (52%), posterior fossa haemorrhage (31%) and subcortical supratentorial haemorrhage (26%). No lesions were found in

patients >46 years with subcortical supratentorial haemorrhage, irrespective of the presence of hypertension.
Conclusions: Underlying vascular lesions are seldom found in a district population compared with a highly selected regional population. Cerebral angiography is unrewarding in older patients with subcortical haemorrhage.

086 A NOVEL SENSITIVE ASSAY FOR AQUEPORIN-4 ANTIBODIES (NMO-IGG)

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Multiple sclerosis (MS) and neuromyelitis optica (NMO) are inflammatory demyelinating diseases. Their treatment and prognosis differ, but on initial examination they can be difficult to distinguish. The discovery that antibodies in the sera of up to 65% of patients with NMO, first described as ''NMO-IgG'' on the basis of an immunofluorescence binding pattern (Lennon *et al* 2004[1]), bind to the water channel aquaporin-4 (AQP4; Lennon *et al* 2005[2]), and their apparent low frequency in MS, offers the possibility for the early discrimination of these two diseases. After confirming that we can detect NMO-IgG by immunofluorescence (Jarius *et al* 2007 in press[3]), we developed a novel immunoprecipitation assay for serum antibodies binding to eGFP-AQP4. The results show high sensitivity and specificity for NMO, with 9/13 NMO sera (70%) and 0/14 MS sera positive. The results suggest that this novel assay will be easier, more quantitative and possibly more sensitive than the immunofluorescence assay for NMO-IgG.

087 LONG TERM USE OF SATIVEX IN MULTIPLE SCLEROSIS CENTRAL PAIN: DOSING AND CHANGES IN CONCOMITANT ANALGESIA

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Background: Little is known of the long term effects of treatments in central pain (CP) in multiple sclerosis (MS).
Methods: Sativex, a whole plant, cannabis based medicine, containing D-9 tetrahydrocannabinol (THC) and cannabidiol (CBD), was investigated in a randomised controlled trial of 66 MS patients with CP. 63 patients (95.5%) entered a long term, open label extension study. Each Sativex oromucosal spray delivered 2.7 mg of THC and 2.5 mg of CBD. Patients self-titrated their dosage.
Results: In the randomised trial, Sativex achieved significant improvements in pain (NRS-11, $p=0.005$ and Neuropathic Pain Scale, $p=0.044$) and sleep disturbance (NRS-11, $p=0.003$) compared with placebo. Mean duration of the open label treatment was 463 days (range 3–917; SD 378). In the 28 subjects (44%) who completed the open label trial, the mean number of sprays taken in the six final treatment days was 6.5 (range 0.5–24.8; SD 5.8). At least one dose was taken by at least one patient in each hour and 26 subjects took less than 11 sprays per 24 h. Concomitant analgesic or potential analgesic doses remained stable in half of the cases, reduced in 3, stopped in 17, increased in 11 and 20 new such medications were commenced.
Conclusion: Long term Sativex use results in flexible dosing and stable concomitant analgesia.

088 NEUROLOGY AT THE FRONT DOOR: PROVIDING AN ACUTE NEUROLOGY SERVICE IN A DISTRICT GENERAL HOSPITAL

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Aim: To evaluate whether it is feasible to provide an acute neurology assessment service in a district general hospital without inpatient neurology facilities.
Setting: Royal Gwent Hospital, a busy 774 bed district general hospital in South Wales.
Methods: For 6 weeks, the neurology team became ''embedded'' with one of the general medical firms and attended the weekday morning ''post-take'' ward round, reviewing all patients presenting with neurological problems. Details of diagnosis, investigation and length of stay of the patients was compared with a matched number of referrals seen prior to the study
Results: From 10 takes, a total of 191 patients were admitted; from these, 43 (22.5%) were identified as having neurological problems. Common presentations included seizure (10 patients, 23.3%), stroke (9 patients, 20.9%) and headache (7 patients, 16.3%). Comparison from prior to the study shows reduction in mean length of stay (6.2 days to 3.9 days; $p<0.05$) and reduction in the amount of cerebral imaging requested. There was no increase in the number of patients being referred for neurology follow-up. A mean of 2.86 h per round was spent reviewing patients.
Conclusions: Although limited, the results suggest that a daily ward round is a feasible and effective approach to moving neurology services closer to the front door.

089 SECULAR TRENDS IN NEUROIMAGING REPORTS IN A DISTRICT GENERAL HOSPITAL

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Background: One in eight of selected neuroimaging reports from general radiologists in a district general hospital (DGH) differ significantly when reassessed by a neuroradiologist (*QJM* 2006;**99**:171–5). We sought to determine whether these results changed in a re-audit.
Objective: To reassess the accuracy of general radiology neuroimaging reports in a DGH.
Methods: CT brain, and MRI brain and spine scans were selected at the discretion of a neurologist for formal reporting by neuroradiologists over an 18 month period. Outcomes were compared with the previous study in the following categories: (a) disagreement frequency in primary diagnosis/finding; (b) disagreement in secondary diagnosis/finding or differential diagnoses; (c) disagreement frequency in primary or secondary findings; and (d) number of further investigations suggested by neuroradiologists.
Results: Scan reports from 180 consecutively selected patients were analysed (90 men, 90 women, mean age 47.7 (SD 18.2) years). Primary outcomes differed in 28 (15.5%), similar to the previous finding of 15.9% (NS). Secondary finding differences improved from 22.4% to 16.1% (52/232 vs 29/180; NS). Combined primary or secondary differences were better (77/232 vs 54/180; NS). Neuroradiologists suggested other investigations in 13.3% (24/232 vs 24/180; NS).
Conclusions: Management of neurology patients in DGHs still requires timely access to neuroradiologists.

090 DEVELOPING ACUTE NEUROLOGY SERVICES IN THE UK: AN ACUTE HEADACHE LIAISON SERVICE

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Introduction: We compared usual care (UC—seen by consultant physician post-take, with option of referral to neurologist) with an Acute Headache Liaison Service (AHLS—seen post-take by consultant neurologist with subsequent inpatient care by consultant physician), and provide data for service development.
Results: 365 (3.3%) of 11 220 medical admissions in 17 months presented with headache (51 assessed by AHLS). 95 (30%) of the remaining 314 were referred to neurology. There was a non-significant trend towards shorter hospital stay (2.8 days UC vs 2.1 days AHLS; $p=0.24$). No significant difference was found in LP, CT or MRI rates. 40% AHLS and 33% UC were reviewed in outpatients. The maximum number of headache cases admitted on any day was 4, with a median of 1 (IQR 0–2). We estimate that an AHLS to an admissions population of 10 000 requires 6 h of consultant time for direct clinical care and 0.5 h per week for outpatient review (excluding time for administration).
Conclusions: An AHLS is a workable method for extending the role of UK neurologists. Costs of additional neurology staff are probably offset by more efficient use of hospital resources.

091 LOCALITY BASED NEUROLOGY CLINICS IMPROVE THE QUALITY OF NEUROLOGICAL CONSULTATION

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The quality of neurological consultation, from both the clinician's and the patient's view, can be improved by seeing patients in clinics nearer their

home in general practitioner surgeries. Since June 2004, a consultant neurologist has seen general neurology referrals in a weekly general neurology clinic held in rotation between four general practitioner surgeries, located in different parts of the catchment area of the neuroscience centre. Patients referred to the neurology department are selected for these locality based clinics if they live nearer to that location than the neuro centre unless, rarely, there is some clinical reason that they should attend the centre. 6–8 new patients and 4–6 follow-up appointments are seen in each clinic.

When compared with patients seen in the neuro centre, there was no difference in case mix in those seen in the locality related clinics. Patient satisfaction with their consultation was markedly higher in those seen in the locality related clinics compared with patients seen in hospital outpatients. The quality of the consultations from the neurologist's point of view was also higher. Patients were satisfactorily managed with shorter consultations, and their waiting times in the clinic were considerably reduced. Informal communications with local general practitioners were also improved.

092 THE EVIDENCE FREE ZONE: MANAGEMENT OF IDIOPATHIC INTRACRANIAL HYPERTENSION BY BRITISH NEUROLOGISTS

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An anonymised questionnaire validated in a pilot study was submitted to all ABN members to assess current practice in idiopathic intracranial hypertension (IIH). Lumbar puncture parameters, preferred treatment and rationale underlying management were analysed.

Of 924 members, 453 (49.02%) returned the questionnaire. CSF pressure was measured in the lying position in 99.2% of cases. Positional manoeuvres were carried out by 33%. Lowering of CSF pressure was influenced by initial reading in 59.6%. A specific volume was drawn by 25.6% of respondents while 52.8% would target a specific closing pressure and only 13.5% would aim for both. Only 17% would routinely repeat the lumbar puncture whereas 59.1% would repeat if symptoms recurred and 48.7% if symptoms failed to resolve. Only 30.5% would repeat the procedure with persisting papilloedema. The improvement was attributed to continuing CSF leak by 37.3% of respondents, to lowering CSF pressure by 36.5%, to volume drainage by 8.6% and to multifactorial reasons by 30.5%. Acetazolamide was the drug of choice in 94.7%.

The results show that most neurologists measure CSF pressure in the lying position and favour acetazolamide as first choice. There is no consensus about all other aspects of IIH management. A structured protocol would facilitate collection of data for evidence based management.

093 BEWARE ALL NEUROLOGISTS: THE FDA'S TOUGH NEW REQUIREMENTS FOR RATING SCALE PERFORMANCE ARE COMING TO A STUDY NEAR YOU SOON

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The US Food and Drug Administration (FDA) is about to publish strict recommendations concerning rating scales used in clinical trials. The European Medicines Evaluation Agency are following suit. Here, we alert the ABN to the FDA's core requirements concerning scale performance, and illustrate why they are essential.

The FDA requires that any rating scale used in clinical trials satisfies minimum statistical requirements for data quality, scaling assumptions, targeting, reliability, validity and responsiveness. The FDA also requires that clinically meaningful content is established through qualitative evaluation.

Our research findings support the need for tough quantitative and qualitative requirements. A literature search shows that state of the art clinical trials continue to use scales proven scientifically poor. Our psychometric evaluations of widely used scales shows that basic assumptions are often not met. Our evaluations identified scales that satisfied statistical tests of adequate performance despite overwhelming qualitative evidence of invalidity.

The FDA guidelines have substantial implications for *all* clinical trials using rating scales. There is strong emphasis on both qualitative and quantitative scale evaluations. Neurologists must increasingly become familiar with, and incorporate, these methods in their studies.

094 REVERSIBLE HYPERTENSIVE CEREBELLAR ENCEPHALOPATHY AND HYDROCEPHALUS

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Introduction: Hypertensive encephalopathy (HTE) commonly presents with headache, confusion, visual disturbance and seizures. Cranial imaging typically reveals parieto-occipital subcortical white matter oedema.
Case report: A 52-year-old man with Holmes–Adie syndrome presented with recurrent vertigo, nausea, ataxia and mild headache. He was alert and orientated. There was persistent severe hypertension. A tonic left pupil was noted. Fundoscopy revealed bilateral papilloedema, A-V nipping and exudate formation. Horizontal pursuit eye movements were broken. There was left finger–nose incoordination, lower limb areflexia and ataxic gait.
Investigations: Cranial MRI revealed swelling of the cerebellum, extensive cerebellar hemisphere signal change, distortion of the fourth ventricle and moderate obstructive hydrocephalus. There was renal impairment and left ventricular hypertrophy. Investigations excluded autonomic failure and secondary causes of hypertension.
Course: Gradual reduction of blood pressure within the first 12 h was achieved with oral modified release nifedipine and was matched by clinical improvement. Repeat cranial MRI 5 days after admission showed almost complete resolution of the cerebellar abnormalities and hydrocephalus.
Discussion: We report a rare presentation of HTE with isolated cerebellar involvement, secondary obstructive hydrocephalus and absence, clinically, of encephalopathic features which was reversible with medical treatment alone without recourse to a CSF diversion procedure.

095 SEMANTIC DEMENTIA WITH MOTOR NEURONE DISEASE PRESENTING WITH FALSE POSITIVE ANTIACETYLCHOLINE RECEPTOR ANTIBODIES

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A 74-year-old woman presented with a 10 day history of progressive dysarthria, dysphagia and dyspnoea eventually requiring admission to intensive care unit. She was treated for confirmed pseudomonas pneumonia and gradually improved following supportive therapy. However, she continued to have bilateral facial and tongue weakness, and poor cough and swallow suggestive of bilateral lower bulbar palsy. The differential diagnosis included myasthenia gravis or the cranio-cervical variant of Guillain–Barré syndrome. However, she had unusual clinical features for both, and neurophysiological assessment did not support either. As antiacetylcholine receptor antibodies were strongly positive, the patient was treated for myasthenia gravis. MRI of the brain did not reveal brainstem abnormality, but showed significant focal left temporal lobe atrophy. In retrospect, her husband commented that her spelling and memory for names and plants have deteriorated over the past year, but her day-to-day memory and personality have remained unchanged. Cognitive assessment revealed fluent speech with significant circumlocutions and loss of semantic knowledge of low frequency words in keeping with a probable diagnosis of semantic dementia. As this condition may be due to underlying motor neurone disease (MND)-type pathology, the most likely cause of this woman's bulbar weakness is believed to be MND.

096 PREVALENCE OF EXCESSIVE DAYTIME SLEEPINESS IN PARKINSON DISEASE MEASURED USING THE EPWORTH SLEEPINESS SCALE

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Background: Daytime sleepiness is an important non-motor symptom in Parkinson disease, having significant adverse effects on quality of life for patients, carers and family members. Symptom measurement raises clinical awareness and may result in more appropriately directed disease management.
Methods: To increase clinical awareness we encouraged routine use of the Epworth Sleepiness Scale (ESS) to measure daytime sleepiness (score range 0–24, normal control $\leqslant$10, narcolepsy range 13–23) for all patients attending our NHS movement disorder clinics.
Results: 843 patients (500 male) with Parkinson disease attended clinics over a 5 year period. 286 patients (190 male), median age 73 years (range 47–93), median duration of parkinsonian symptoms 5.1 years, were evaluated with the ESS. The median ESS score was 9 (range 0–23). 37.1% of patients scored $>$10 and in 23.1% the score was $\geqslant$13. In the 75 patients who had symptom duration of less than 3 years, median score was

7 (range 0–22). In the 66 patients who had suffered symptoms for 10 or more years, median score was 10 (range 0–23).
Conclusions: Excessive daytime sleepiness has a high prevalence in patients with Parkinson disease. The ESS is quick and easy to administer and should form part of routine clinical assessment in Parkinson disease.

097 MULTIMODAL FUNCTIONAL AND STRUCTURAL IMAGING TO GUIDE EPILEPSY SURGERY

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Aim: To use structural and functional imaging to visualise epileptic activity and motor function to guide resections in focal epilepsy.
Methods: Three patients with refractory focal epilepsy were studied with MRI, including functional MRI (fMRI) and fluorodeoxyglucose–positron emission tomography (FDG–PET), prior to investigation with intracranial EEG.
Results: Case 1: MRI showed left frontal focal cortical dysplasia (FCD) anterior to the motor cortex mapped with motor fMRI. EEG–fMRI recorded no interictal discharges (IED). Invasive EEG monitoring and stimulation confirmed seizure onset in the FCD, anterior to the motor cortex. Lesionectomy resulted in seizure control and no deficit.

Case 2: MRI showed FCD in the right post-central gyrus adjacent to the primary motor cortex mapped with fMRI. EEG–fMRI recorded no IED. Invasive EEG monitoring confirmed seizure onset in the FCD, but hip flexion on stimulation in the same location precluded resection.

Case 3: MRI showed probable FCD in the left superior frontal gyrus with FDG–PET hypometabolism seen in the same area.

EEG-fMRI showed IED correlated BOLD signal change bilaterally, posterior to the primary motor cortex mapped on motor fMRI. Intracranial EEG recordings and stimulation are planned.
Conclusion: Multimodal structural and functional brain imaging provides useful data for planning intracranial EEG recordings and neocortical resections in focal epilepsy.

098 MULTIPLE SCLEROSIS SERVICES IN THE UK: BARRIERS TO IMPROVEMENTS IN SERVICES

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The NICE Multiple Sclerosis (MS) Management Guidelines were launched in November 2003. Recent research undertaken by the Royal College of Physicians in conjunction with the MS Trust reports on implementation of these guidelines in England. A triangulation methodology was used to capture data from the SHAs, PCTs, NHS Trusts and people with MS. The results demonstrate that information provision alone does not change practice, coordination across services will be critical for success and that while there are pockets of excellence, there are real gaps in service provision. These data will form the baseline data for a regular 2 yearly assessment, using the model of the RCP stroke audit, which has been so instrumental in improving stroke services in the UK.

The presentation will also report on research commissioned by the MS Society, which identifies barriers to people with MS getting access to the appropriate health care professional in a timely fashion. In particular, the research identifies the complexity of obtaining an appropriate referral from general practice.

Both research projects provide useful data to demonstrate a lack of resources and management commitment to neurology, but they also provide evidence of strategies to improve the situation.

099 PARKINSON DISEASE: A DUAL HIT HYPOTHESIS

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Background: Lewy body disease (LBD) pathology (Lewy neurites/bodies) in classical Parkinson Disease (PD) probably commences simultaneously in the medullary vagal motor nucleus and olfactory bulb. We suggest a common pathological mechanism to explain how such anatomically separate structures become involved early in PD.
Literature: Olfactory impairment: there is extensive evidence for this, whether measured by psychophysical, neurophysiological or patho-anatomical methods. Large prospective studies imply that olfaction is damaged well before motor symptom onset. Vagal disorder: the vagus is significantly impaired, as shown by heart rate variability, dysphagia or gastric dysfunction, and medullary pathology. Prospective assessment of bowel habit indicates constipation is a premotor sign. LBD pathology occurs early in the gastric enteric plexus where vagal motor fibres terminate.
Conclusion: We propose that a pathogen, possibly viral, damages the nasal olfactory neuroepithelium, causing olfactory impairment, and is then swallowed in secretions. After entering the gastric enteric plexus, it travels retrogradely along vagal motor fibres to the medulla. Subsequent rostral progression to the substantia nigra results in classical PD features.

100 MENINGEAL B CELL FOLLICLES IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS ASSOCIATE WITH EARLY ONSET OF DISEASE AND SEVERE CORTICAL PATHOLOGY

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Identification of organised B cell follicles in the cerebral meninges in patients with multiple sclerosis (Serafini 2004) supports the concept that plasma cell differentiation can be sustained locally within the central nervous system and contributes to the establishment of a compartmentalised humoral immune response, the classic hallmark being intrathecal antibody production.

We studied 29 randomly selected secondary progressive multiple sclerosis (SPMS) cases to determine the association of follicles with the clinical and neuropathological features of MS.

Follicles were detected in the meninges entering the cerebral sulci in 12 of 29 SPMS cases. SPMS cases with follicles significantly differed from those without, with respect to a younger age at MS onset, irreversible disability and death. Follicles were associated with severe MS independent of high early relapse rate, a known factor to be associated with a poor outcome. Histologically they had more pronounced demyelination, microglia activation and loss of neurites in the cerebral cortex. All meningeal B cell follicles were found adjacent to large subpial cortical lesions, suggesting soluble factors diffusing from these structures could have a pathogenic role.

This supports a novel mechanism whereby ectopic B cell follicles developing in the MS meninges exacerbate the detrimental effects of humoral immunity with a subsequent major impact on outcome.

101 MITOCHONDRIA AND PRIMARY OLIGODENDROCYTE DYSFUNCTION IN MULTIPLE SCLEROSIS

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Background: Oligodendrocyte loss is a well recognised feature of MS. Although the degree of oligodendrocyte loss and demyelination correlates with inflammation in MS, effector mechanisms appear heterogeneous. The association of primary oligodendrocyte dysfunction and hypoxia inducible factor-1alpha suggests a role for mitochondria in the pathogenesis of MS.
Aims and methods: To determine the expression of nuclear and mitochondrial DNA encoded respiratory chain complex subunits, using immunohistochemistry, in acute (n = 20) and chronic (n = 10) MS tissue and controls (n = 12). The immunoreactivity of porin (a mitochondrial marker) and subunits of respiratory chain complex-I, complex-II and complex-IV was quantitated.
Results: Complex-IV subunit-I (COX-I, a catalytic component) was decreased in non-demyelinated WM and early stages of acute MS lesions in association with primary oligodendrocyte dysfunction. Furthermore, COX-I loss was identified in axons and astrocytes in MS lesions containing oligodendrocyte apoptosis, where the expression of inducible nitric oxide synthase is prominent.
Conclusion: The state of energy depletion in the early stages of acute MS lesions, judged by COX-I immunoreactivity, may play a role in the dysfunction of oligodendrocytes. The protection of respiratory chain complex-IV may be of therapeutic value in MS.

102 HIPPOCAMPAL VOLUME IS AN INDEPENDENT PREDICTOR OF COGNITIVE PERFORMANCE IN PURE CEREBRAL SMALL VESSEL DISEASE

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Background: Cerebral small vessel disease (SVD) is a major cause of cognitive impairment. The importance of hippocampal atrophy is less clear than in Alzheimer's disease. Attempts to study this in sporadic SVD are hampered by age related degenerative pathology. To clarify the role of hippocampal atrophy, we studied the genetic disease CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a model of pure cerebral SVD.
Methods: 144 patients were recruited in two centres and underwent clinical and cognitive assessment and MRI. Hippocampal volumes were measured on volumetric T1 weighted images. Normalised brain volume, and volumes of lacunar and diffuse white matter lesions (WML) on FLAIR were also quantified.
Results: Hippocampal volumes were reduced in demented patients (n = 21) (mean of left and right 2272 (333) mm^3 vs 2642 (349) mm^3; $p<0.001$) and correlated with the Mini-Mental Score Examination ($r=0.30$, $p<0.001$) and Mattis Dementia Rating Scale ($r=0.40$, $p<0.001$). Hippocampal volume correlated with normalised brain volume ($r=0.39$, $p<0.001$) and lacune volume ($r=-0.23$, $p=0.008$), but not with WML. In a multivariate model, hippocampal volume was an independent predictor of Mattis performance (beta 0.26, $p=0.001$). In the subgroup aged less than 60 years, hippocampal volume was reduced in dementia and remained an independent predictor of global cognitive function.
Conclusions: Hippocampal atrophy is an integral component of pure SVD and is an independent predictor of cognitive status.

103 SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS HAS MORE AXONAL LOSS IN THE SPINAL CORD THAN PRIMARY PROGRESSIVE

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Introduction: The pathological substrate of progressive disability in multiple sclerosis (MS) is hypothesised to be axonal loss. Distinct pathological and radiological features of patients with primary progressive MS (PP) have raised the question as to whether they actually represent a separate clinical entity. To date, pathological studies of axonal damage in PPMS have not been reported. Furthermore, few studies of spinal cord pathology in MS have had detailed clinical data.
Objectives: To compare corticospinal tract (CST) axonal loss in primary and secondary progressive (SP) MS.
Methods: Autopsy material was derived from 25 cases of SPMS, 7 cases of PPMS and 5 controls. Transverse sections of cervical spinal cord were used to perform quantitative analysis of CST axons.
Results: Both PPMS and SPMS cases demonstrated CST axonal loss in comparison with controls ($p=0.004$). Compared with PPMS cases matched for age and disease duration, cases with SPMS showed a 35% reduction in CST axonal numbers ($p=0.02$). Grey and white matter demyelination was also more extensive in SPMS compared with PPMS.
Conclusion: In this first report of axonal damage in PPMS, substantially less axonal loss and demyelination have been found in the cervical spinal cord compared with SPMS. This suggests that different pathogenetic mechanisms may account for the progressive disability seen in the two disease types.

104 RETROSPECTIVE ANALYSIS OF RITUXIMAB TREATMENT OF 24 CASES OF NEUROMYELITIS OPTICA

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Objective: To assess relapse frequency and disability in patients with neuromyelitis optica (NMO) treated with rituximab (RTX).
Background: NMO is an inflammatory demyelinating disease that causes attack related disability. Treatments to prevent relapses are limited and anecdotal. RTX appeared to reduce relapse frequency in eight patients (Cree *et al*).
Design: Retrospective review of 24 cases of NMO from five centres in the USA and UK.
Results: 3 men and 21 women were treated. 22 patients had NMO and 2 patients had relapsing myelitis. RTX was initiated in 22/24 patients because of failure of other medications. All patients received 2–4 infusions at 375 mg/m^2 at weekly intervals. The median (range) number of infusion cycles was 2 (1–5). The median (range) follow-up time after initiating treatment with RTX was 22 months (4–40).

18 patients continued to receive RTX at the last follow-up. Six patients discontinued, three because of relapses. Two patients died of infections 10 and 12 months after the last RTX infusion. The post-treatment relapse rate (0.2, range 0–3.2) was lower than the pretreatment rate (1.6, range 0.5–5) ($p=0.0002$, signed rank test). Expanded Disability Status Scale scores of 22 patients (91%, excluding those who died) stabilised or improved.
Conclusions: RTX appears to reduce relapses and improve or stabilise disability in NMO.

105 ATROPHY OF MEDIAL TEMPORAL LOBE CONNECTIONS IN UNILATERAL TEMPORAL LOBE EPILEPSY: A TRACTOGRAPHY BASED STUDY

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Aim: Temporal lobe epilepsy (TLE) is associated with disrupted memory function, and memory impairment is common following anterior temporal lobe resection. The structural changes underlying this memory impairment have not been demonstrated previously, and may assist surgical planning to minimise deficits.
Methods: We performed magnetic resonance tractography in 18 patients with unilateral TLE undergoing presurgical evaluation and in 10 healthy controls. A seed point in the anterior parahippocampal gyrus was selected to trace the white matter connections of the medial temporal lobe. Correlations were performed between volume and mean fractional anisotropy (FA) of the connections, and pre- and postoperative material specific memory performance.
Results: There was no significant difference between the left and right sided connections in controls. In the left TLE patients, connections ipsilateral to the epileptogenic region were found to be significantly reduced in volume and mean FA compared with the contralateral region. Significant correlations were found in left TLE patients between left and right FA, and verbal and non-verbal memory, respectively.
Conclusions: Tractography demonstrated the reorganisation of white matter pathways that may underlie impaired memory function in TLE. A detailed knowledge of the integrity of these connections may be useful in predicting memory decline in chronic temporal lobe epilepsy.

106 MULTIPLE SCLEROSIS AND RETENTION OF EMPLOYMENT: EXPERIENCE WITHIN THE RISK SHARING SCHEME

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Background: Retention of employment is a key issue in multiple sclerosis (MS) for both social functioning and psychological wellbeing, and also has financial implications for individuals, their families and the state.
Objective: To determine employment status in MS patients receiving disease modifying therapy.
Methods: A cohort of 1273 patients across 28 UK centres participating in the MS risk sharing scheme completed a questionnaire exploring disease costs and quality of life. Current and recent changes to employment status, income bracket and benefit receipts were recorded.
Results: In a cohort of patients with a mean age of 40 years and disease duration of 8 years, only 45% were currently employed. 8% reported being absent from work because of MS and 13% retired as a result of illness. 24% of the entire sample reported a change in employment status due to their MS during the past year; of these, 30% stopped work altogether and 40% reduced their hours. 11% of partners had to change their employment arrangements.
Conclusion: Despite more widespread availability of disease modifying therapies and recent disability legislation, MS continues to have a major impact on employment status in the UK.

107 ASPERGILLUS PACHYMENINGITIS PRESENTING AS ACUTE LOSS OF VISION AND HEADACHE IN A DIABETIC

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A 73-year-old diabetic man was referred to our centre with sudden loss of vision in the left eye and headache. He was commenced on steroids with a presumed diagnosis of temporal arteritis in view of the clinical features and elevated inflammatory markers, erythrocyte sedimentation rate and C reactive protein. He continued to deteriorate with further visual loss on the opposite side and a temporal artery biopsy was negative. Neuroimaging of his brain demonstrated extensive meningitis with abnormal dural enhancement around the optic nerves. CSF analysis was unremarkable except for mildly raised protein. A meningeal biopsy showed Aspergillus fumigatus meningitis and the pus drained from the left frontal sinus grew Aspergillus. Voriconazole caused adult respiratory distress syndrome and he developed hepatic dysfunction from antifungal therapy with amphotericin B and caspofungin. He eventually died of multiorgan failure and multiple cerebral infarcts. Aspergillus infection is predominantly a manifestation of impaired host defences but it does occur rarely in immunocompetent hosts and is difficult to diagnose. Cerebral aspergillosis has a significant mortality and poor prognosis in spite of prompt diagnosis and treatment. CNS aspergillosis is secondary to direct spread from the nasal sinus or it could be due to a haematogenous spread from the lungs and gastrointestinal tract.
Conclusion: CNS fungal infection should be considered in the differential diagnosis of acute visual loss in both immunosuppressed and immunocompetent patients and it can mimic temporal arteritis.

108 RASCH ANALYSIS OF THE MODIFIED FATIGUE IMPACT SCALE IN MULTIPLE SCLEROSIS

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Background: The 21 item, Modified Fatigue Impact Scale (MFIS) has been recommended as an outcome measure for use in multiple sclerosis (MS), and is commonly used to generate an overall score of fatigue.
Objective: To assess the MFIS for the fundamental requirements of measurement (ie, unidimensionality) order and additivity by application of the Rasch measurement model.
Method: The MFIS was sent by post to patients with clinically definite MS in two centres in the UK. Analysis was based on 415 records (55% response).
Results: The 21 item scale did not fit the Rasch model. A basic fit was achieved by deleting four items but six items displayed differential item functioning (DIF) by disability and five items by disease type. In addition, post hoc tests of unidimensionality were not satisfied. An exploratory factor analysis suggested the presence of at least two factors.
Conclusion: The MFIS does not have unidimensionality which suggests that it may be unsuitable as a measurement tool for overall fatigue impact. Without undimensionality, order and additivity cannot be inferred. The DIF by disability and disease type may be confounding comparisons of fatigue between different MS patient groups.

109 TRIGEMINAL INVOLVEMENT IN MULTIPLE SCLEROSIS USING HIGH RESOLUTION MRI AT 3 T

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Background: Trigeminal neuralgia/sensory disturbance is common in multiple sclerosis (MS). Recent literature suggests that signal abnormalities in the cisternal trigeminal nerve and pontine root entry zone are seen in approximately 3% of patients, using conventional diagnostic MRI.
Objective: To determine the prevalence of trigeminal lesions using high resolution MRI at 3 T.
Method: 47 patients with clinically definite MS, chosen at random from an MS database, and 9 healthy controls underwent MRI on a Siemens 3 T Trio machine. Three, three-dimensional sequences of T2 TSE (turbo spin echo), T2 FLAIR (fluid attenuated inversion recovery) and T1 IR (inversion recovery) were acquired in the coronal plane. The sequences were of contiguous 1 mm slices with inplane resolution of up to 0.5 by 0.5 mm. Images were read by both a neurologist and a neuroradiologist. Any clinical history of trigeminal symptoms was determined for all subjects.
Results: 11 patients (23%) had high signal in the trigeminal nerve, root entry zone or pontine nucleus. No comparable changes were seen in the healthy controls. MRI changes did not correspond to clinical symptoms (χ^2 probability 0.712).
Conclusion: High resolution MRI at 3 T improves detection of trigeminal abnormality in MS. MRI involvement does not correspond to trigeminal symptoms.

110 THE MYSTERY OF THE LOST MEMORY: ACUTE DISSEMINATED ENCEPHALOMYELITIS, MULTIPLE SCLEROSIS OR SOMETHING ELSE?

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A 52-year-old woman presented with acute headache, amnesia and confusion in 2002. Brain CT showed low attenuation in both occipital areas. CSF contained 8 white cells, normal protein and glucose levels. Intravenous acyclovir was started for possible viral encephalitis. PCR of CSF was negative for common viral pathogens. Further tests reported multiple T2 periventricular white matter lesions on brain MRI, oligoclonal bands in CSF only and visual evoked potentials demonstrating bilateral optic nerve demyelination. She was diagnosed with acute demyelinating encephalomyelitis.

Headaches, cognitive disturbance, frequent spatial disorientation, mild diarrhoea, xerostomia and xerophthalmia persisted for 3 years. Repeated investigations showed positive antinuclear (1:640), positive anti-Ro and equivocal anti-La antibodies. Serum immunoglobulins were raised (IgG 30.7 g/l). Repeated lumbar puncture showed only one oligoclonal band in CSF. A positive Schirmer's test confirmed the diagnosis of primary Sjogren's syndrome (PSS). She was treated with high dose intravenous methylprednisolone. Follow-up brain MRI showed reduced lesion load, and neuropsychology testing demonstrated memory improvement.

PSS is a common autoimmune disorder, although patients rarely exhibit focal or diffuse central nervous system involvement. Atypical presentations with neuropsychiatric or spinal cord symptoms have a variable response to immunosuppressive therapy.

111 SUCCESSFUL TREATMENT OF SEVERE ANTINEUTROPHIL CYTOPLASMIC ANTIBODY ASSOCIATED CNS VASCULITIS WITH A RITUXIMAB BASED REGIMEN

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We report successful treatment of antineutrophil cytoplasmic antibody (ANCA) associated cerebral vasculitis with rituximab.

A 54-year-old woman presented with acute renal failure requiring dialysis and was shown to have a rapidly progressive glomerulonephritis due to PR3-ANCA associated vasculitis. Despite treatment with high dose glucorticoid, oral cyclophosphamide and plasma exchange, she remained dialysis dependent, and subsequently developed generalised seizures and fall in conscious level, necessitating transfer to the intensive care unit. MRI, lumbar puncture and EEG were consistent with acute vasculitis, and infective encephalitis was excluded. She was then treated aggressively with rituximab and further intravenous methylprednisolone after which her condition rapidly improved. By the time of discharge from hospital, 30 days after the onset of neurological symptoms, she had no residual neurological deficit and was dialysis independent.

Rituximab is a monoclonal anti-CD20 antibody. A possible mechanism of action is B cell depletion thus ''switching off'' further ANCA production which may be pathogenic. We believe this to be the first report of successful treatment with rituximab in acute ANCA related CNS vasculitis, suggesting a new strategy for treatment resistant cases.

112 SELECTING THE RIGHT RATING SCALE: DO NEUROLOGISTS HAVE TO HAVE WHAT THEY'RE GIVEN OR CAN THEY GET WHAT THEY NEED?

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Neurological studies require rating scales that meet different needs. For example, clinical trials typically need high precision in a specific range whereas observational studies require less precision across a fuller range. New measurement methods (Rasch analysis) provide the unique opportunity to construct scales that deliver this flexibility. This is not possible with traditional psychometric techniques that rely on fixed length scales. This study demonstrates measurement flexibility by constructing, comparing and

contrasting four versions of a new scale for Friedreich's ataxia (FA), the FA Impact Scale (FAIS).

In addition to the long form version (117 items; suitable for clinical trials), we constructed: a 60 item version for observational studies (FAIS-OBS); a 60 item version for cohort studies of extremely disabled patients (FAIS-EXT); and a 60 item version for patients at the lower end of disease impact (FAIS-MLD). Rasch analysis (n = 307) enabled equating all four FAIS versions on the same metric, comparison of the extent to which measurement equivalence was confirmed, showed their relative ranges and precisions of measurement, and proved targeting to different disability levels.

This study shows just one of the many clinical advantages of using new psychometric methods, such as Rash analysis, to construct rating scales. Hence neurologists can now get what they need.

113 POEMS SYNDROME MIMICKING SYSTEMIC VASCULITIS

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A 57-year-old man developed a painful sensory neuropathy, proteinuria and ankle oedema. There was electrophysiological evidence of an axonal sensory neuropathy; protein electrophoresis, inflammatory markers and autoantibodies were normal or negative. Sural nerve biopsy showed axonal loss and fibrinoid necrosis of small vessels; renal biopsy demonstrated thrombotic microangiopathy. He developed transient ischaemic attacks which resolved with prednisolone and clopidogrel, following which his neuropathic symptoms also improved. A diagnosis of vasculitis was made.

Over 3 years his neuropathy worsened despite treatment with cyclophosphamide and plasma exchange. He suffered further cerebral and peripheral arterial thromboses, and received warfarin. Four years into the disease he had distal motor weakness and had developed papilloedema. Investigations revealed restrictive lung disease, splenomegaly, thrombocythaemia, endocrinopathy and, for the first time, a low titre IgA lambda paraprotein. Repeat electrophysiology showed a severe demyelinating neuropathy. The diagnosis was revised to POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome. No plasmacytoma has been identified.

Following reports implicating vascular endothelial growth factor (VEGF) in the pathogenesis of POEMS syndrome, serum VEGF was measured and was markedly elevated (6451 pg/ml; normal <100). Treatment with bevacizumab, a monoclonal antibody against VEGF, reduced serum VEGF to normal levels and in combination with ongoing immunosuppression and tamoxifen his condition has stabilised.

114 WHEN CLASSICAL MIGRAINE IS NOT CLASSICAL MIGRAINE

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Case: A 48-year-old woman presented to A&E with headache and visual disturbance 5 days following a road traffic accident. She represented 2 days later with headache and transient dysarthia. Neurological examination and CT brain were normal. Past history included migraine with visual aura and her symptoms were similar but more frequent and severe.

Results: MRI of the brain showed some non-specific changes. Carotid Doppler ultrasound showed markedly reduced internal carotid flow velocities bilaterally and MR angiogram showed bilateral complete occlusion of the extracranial internal carotids. A diagnosis of spontaneous traumatic carotid artery dissection was considered. Subsequent four vessel angiography revealed diffuse concentric narrowing with almost complete occlusion of both internal carotids. The external carotids and the posterior circulation provided collateral supply. On the left internal carotid there was a definite suggestion of beading. Renal angiography on the left showed beading pathognomic of fibromuscular dysplasia.

Conclusion: Although difficult to demonstrate because of diffuse concentric narrowing, it is likely that traumatic dissection completed occlusion of the internal carotids already chronically narrowed by longstanding fibrodysplastic change. This case however is distinctly unusual in that there was no neurological deficit despite complete occlusion of the anterior circulation and the only persistent symptom being ''migrainous headache''.

115 CLASSIFICATION OF MINOR STROKE BY CLINICAL AND ACADEMIC PHYSICIANS: A STUDY OF INTER- AND INTRAOBSERVER RELIABILITY

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Introduction: The Oxfordshire Community Stroke Project (OCSP) and Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classify stroke by affected vascular territory and aetiology, respectively. Use of these classifications in minor stroke outpatients is unexplored but has relevance to clinicians and academics.

Methods: Four observers of differing seniority (two clinicians and two academics) were allocated written case summaries on 45 minor stroke patients presenting to NHS clinics. Each observer independently rated these summaries twice using OCSP and subsequently twice using TOAST. Intra- and interobserver reliability was calculated using unweighted Cohen's kappa (κ).

Results: OCSP interobserver reliability was good ($\kappa = 0.64$) and intraobserver reliability varied from moderate to excellent ($\kappa = 0.60$ to 0.83). For TOAST classification, brain/vascular imaging was available in all patients, electrocardiograms in 92% and echocardiograms in 44%. TOAST interobserver reliability was moderate ($k = 0.42$) and intraobserver reliability varied from moderate to excellent ($\kappa = 0.48$ to 0.82).

Conclusions: Neither classification was consistently reliable, although OCSP had greater inter- and intraobserver reliability. This may reflect our greater familiarity with OCSP, incomplete investigational data for TOAST or greater complexity of TOAST criteria. We suggest the TOAST classification may be problematic in this setting without complete diagnostic workup and further training for both clinicians and researchers.

116 RATING SCALE RESPONSIVENESS: ITS TIME TO CHANGE THE WAY WE MEASURE CHANGE

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Clinical trials require rating scales that detect change. Previously, we found that the Barthel Index (BI) underestimates change associated with neurorehabilitation (n = 1396), and hypothesised this was due to its crude response categories.

We tested this hypothesis by determining if a similar scale with more response categories (Functional Independence Measure, FIM) was more responsive, in the same sample. We found the FIM had smaller ceiling effects than the BI (5.4% vs 27.8%) and detected change in more people (n = 151). Nevertheless, effect sizes for the two scales were almost identical (FIM = 0.74; BI = 0.77), implying similar responsiveness. This counter intuitive finding questions the suitability of effect sizes as indicators of responsiveness.

Therefore, we re-explored our data using a sophisticated psychometric method (Rasch analysis) which enabled legitimate examination of change at the individual person level, rather than simply at the group level. The FIM detected significant change in nearly twice as many people as the BI (54% vs 30.4%), and recorded less people as unchanged (4.4% vs 13.3%).

This study demonstrates the following: superior responsiveness of the FIM; limitations of effect size calculations; and added value of Rasch analysis for examining rating scale responsiveness. Its time to change the way we measure change.

117 SUSTAINING ATTENTION IN HEMISPATIAL NEGLECT FOLLOWING STROKE

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Hemispatial neglect after right hemisphere stroke is associated with leftward inattention. We hypothesise that one underlying deficit may be an inability to sustain attention over time, particularly for leftward items.

Right hemisphere stroke patients with neglect (n = 9) were compared with elderly and stroke control participants, on short (10 min) novel tests of sustained attention. Sequences of stimuli were presented either centrally or just left or right of fixation. Subjects responded to targets—of high or low salience—but withheld responses to non-targets.

Neglect patients made significantly more errors which increased with time, even when stimuli were presented centrally and for high or low salience targets. Importantly, their errors were modulated by the location of the previous stimulus. Left targets preceded by left sided stimuli produced far more errors than if preceded by a right stimulus, so items to the left

could be detected but this depended on whether attention had previously been deployed to the left or right.

These findings demonstrate that neglect patients have deficits in sustaining attention over time to salient stimuli, even when there is no spatial component to the task. They show that difficulty in maintaining attention to left sided stimuli may be a critical component.

118 EARLY POSTOPERATIVE ANXIETY AND DEPRESSION AFTER EPILEPSY SURGERY

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Aim: To determine the frequency of early depression and anxiety in patients undergoing temporal lobectomies for refractory epilepsy.
Methods: Patients operated on for refractory temporal lobe epilepsy between 2004 and 2006 were included. Exclusion criteria were extratemporal epilepsy and the presence of a glioma.
Results: 27 patients were included (11 female, 16 male), mean age 32.5 years (range 18.5–48.5). 24 had hippocampal sclerosis or gliosis and 3 had caveromas. 12 had operations on the left and 15 on the right side. 3 had early postoperative convulsions and 1 continued to have habitual seizures, although less frequently.

9 patients (33%) had marked affective disturbances after surgery. 5 were female and 4 were male. 6 patients experienced depression, 1 took an overdose of paracetamol and 1 was found to be intoxicated with carbamazepine in the context of a possible overdose. 3 patients suffered anxiety (1 had early postoperative seizures).

In all patients the symptoms occurred in the weeks after discharge and improved spontaneously.
Conclusions: Affective disturbances were detected in one-third of all patients undergoing temporal lobectomies. Affective disturbances occurred in seizure free patients and affected both men and women.

119 TRANSCRANIAL DIRECT CURRENT STIMULATION: A POTENTIAL TOOL FOR REHABILITATION?

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Transcranial direct current stimulation (tDCS) is a non-invasive technique that improves hand function in stroke study patients. Anodal stimulation increases excitability whereas cathodal stimulation decreases it. Improvements are achieved using anodal stimulation to the affected hemisphere or cathodal stimulation to the contralateral hemisphere. Despite measuring a peripheral response to cranial stimulation, the response of the cortex is unclear. Thus we have studied the cortical effects of tDCS in healthy controls using functional MRI (fMRI).

Eight subjects performed a motor task before and after 10 min of 1 mA stimulation to the left primary motor cortex (M1). fMRI data were acquired using a standard EPI sequence and analysis was performed using the FMRIB Software Library.

Anodal stimulation produced significantly increased activation in stimulated M1 whereas cathodal stimulation produced a significant increase in contralateral M1 and premotor areas.

Activation of the underlying cortex by anodal stimulation helps explain previous effects on peripheral neurophysiology and hand tasks. Increased activation in the unstimulated hemisphere following cathodal stimulation may represent adaptive compensation.

Our results suggest that anodal stimulation of an affected M1, or cathodal stimulation of an unaffected M1, would both result in increased activity in the affected M1. Restoring the motor cortical balance following stroke may therefore improve hand function.

120 LONGITUDINAL STUDY OF EXPRESSION OF CCL2 AND CXCL10 IN THE SERUM OF PATIENTS WITH MULTIPLE SCLEROSIS

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Chemokines are chemoattractant cytokines which are involved in the directional migration of cells from the blood into the CNS in conditions such as multiple sclerosis (MS). Two key chemokines, CCL2 and CXCL10, have been identified in the CNS in MS at inflammatory foci. We have undertaken a 12 month study of 21 patients with relapsing remitting MS and 10 healthy volunteers. Blood samples were collected from all subjects at 2 monthly intervals and at any time when clinical relapses were reported. CCL2 and CXCL10 levels were measured in serum by ELISA. During the study period, 14 patients had clinical relapses (total of 20 relapses) and were defined as the active group. The remaining seven patients were defined as the stable group. Mean expression of CCL2 in both the active and stable MS groups was significantly lower than in healthy controls ($p<0.001$). Mean expression of CXCL10 in all MS patients was significantly lower than in healthy controls ($p=0.004$). The level of expression of CCL2 and CXCL10 was significantly lower following clinical relapses in the active MS group ($p=0.04$ and 0.009, respectively). The chemokines CCL2 and CXCL10 are important markers of disease activity in MS and might guide future MS therapies.

121 A SAFETY AND FEASIBILITY STUDY OF INTRAVENOUS AUTOLOGOUS BONE MARROW STEM CELLS IN MULTIPLE SCLEROSIS

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Regenerative cell therapy is an attractive prospect for neurological diseases where there are few treatment options. However, controlled clinical trials in Parkinson disease were disappointing, and the ethical and practical problems associated with the use of embryonic tissue have slowed progress. Understandably, this stimulated the search for alternative sources of cells.

That adult bone marrow derived cells can express neuroectodermal markers generated much excitement; bone marrow is a readily accessible source of autologous adult stem cells that haematologists have exploited clinically for decades. Although the validity of reports of in vitro (trans)differentiation has been questioned, demonstration of functional benefit and histological repair in animal models of neurological disease, including experimental demyelination, is encouraging and raises the possibility that transplanted cells may not simply replace lost cells but can exert beneficial effects via alternative mechanisms, including provision of trophic factors or immune modulation–reparative neuroprotection.

The extensive safety data from the use of bone marrow in clinical haematology and oncology has facilitated the rapid translation of basic research into clinical trials, most notably in myocardial infarction and stroke. Here we report the commencement of a safety and feasibility study of autologous bone marrow transplantation in patients with multiple sclerosis.

122 POLYMERASE GAMMA MUTATION PRESENTING AS EPILEPSIA PARTIALIS CONTINUA

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Polymerase gamma mutations cause a wide spectrum of illnesses, ranging from isolated myoclonus to severe encephalopathy. We report a young girl with refractory epilepsia partialis continua secondary to a mutation of POLG producing a W748S substitution. The patient presented initially aged 16 years with intermittent jerking of the left leg. Investigations revealed no abnormality. She represented a year later with generalised seizures. The course of illness spanned 9 months with multiple episodes of status refractory to all antiepileptic medications. Although initial examination was normal she later developed rotatory nystagmus, bilateral cortical blindness and areflexic lower limb weakness. Blood and CSF lactate were normal although MR spectroscopy showed a lactate peak in the posterior fossa. Serial MRI scans revealed transient areas of high signal in the right thalamus, cerebellum, occipital lobes and right parietal lobe. Muscle biopsy showed no ragged red fibres and COX stains were normal. Extensive investigations, including tests for vasculitis, porphyria, Whipple's disease and common metabolic diseases, were normal. Although she had deranged liver function, there were no abnormalities of the liver on imaging or biopsy. She died soon after diagnosis. Her parents have subsequently been found to be heterozygous for the same mutation.

123 THE GENETICS OF ANTIEPILEPTIC DRUG RESPONSE IN FOCAL EPILEPSY: A LARGE CANDIDATE GENE STUDY

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Refractory epilepsy is a significant clinical problem and may be influenced by genetic factors. Here we operationally defined extremes of drug response and undertook a genetic association study for common variants in candidate genes which may influence drug response.

We identified 186 refractory patients (defined as those who had undergone or been assessed for resective epilepsy surgery). 121 responsive patients were identified who had achieved seizure freedom for 1 year within 6 months of antiepileptic drug change, with prior seizure frequency of ⩾3 per year. We genotyped 4067 single nucleotide polymorphisms (SNPs) in 284 candidate genes relevant to epilepsy predisposition and drug response. All putatively functional SNPs were genotyped; 203 highest priority genes were tagged to represent all common variation. Association analysis compared allele frequencies between the two groups using a standard c^2 test. 138 SNPs showed association at the $p<0.05$ level. The lowest p value observed (0.0015) was for an intronic SNP in GRM4 without known function. No SNPs remained significantly associated after correction for multiple testing, but SNPs of interest are being genotyped in a replication cohort.

124 MYTHS ABOUT RATING SCALES: THERE IS A MAGIC NUMBER OF RESPONSE CATEGORIES

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There is a widely held, frequently quoted and often applied belief that rating scale items should have between five and seven response categories. This myth could be propagated because it was an untestable assumption. But no longer. We and others have demonstrated, using new psychometric analysis methods, that this assumption is often not satisfied and, as a consequence, rating scales frequently have too many response categories. This implies they are not working as intended.

Here we demonstrate, using data from a new type of scale (item bank) for people with multiple sclerosis (MS), how new methods can be used to produce empirically determined response categories that do work as intended.

There were three stages. (1) Three focus groups generated different versions for the response categories. (2) These versions were piloted in people with MS and two clinically meaningful versions were shortlisted. These had four and five response categories respectively. (3) These two versions were tested in a postal survey of n = 431 patients. Rasch analysis clearly identified the superiority of the four response category version.

Is there a magic number of response options? Of course—but it's disease, health construct and rating scale dependent, and must be determined empirically.

125 MULTIPLE SCLEROSIS IN AN ADRENOLEUCODYSTROPHY CARRIER

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A 30-year-old female known to be a heterozygous carrier of x linked adrenoleucodystrophy (ALD) presented with a history of eight episodes of right sided numbness and weakness lasting weeks at a time with almost full recovery over a period of 4 years. She had no other significant past medical history. On examination, she had mild pyramidal weakness of her right leg with brisk tendon reflexes, flexor plantars and impaired proprioception in her right arm.

Cranial MR imaging showed areas of high signal in a periventricular distribution in keeping with demyelination. Her cerebrospinal fluid showed two white cells with positive oligoclonal bands. Her visual evoked responses were normal. Very long chained fatty acids were raised in serum and she was positive for ABCD1 mutation.

A diagnosis of relapsing remitting multiple sclerosis was established and she was started on interferon beta 1a. Her condition has since remained stable with no more than one sensory relapse over a period of 2 years.

This case is particularly interesting considering the fact that female carriers of ALD may present with symptoms, which are often mistaken for multiple sclerosis. To our knowledge, there is only a single case report in the literature similar to this patient.

126 ASSESSMENT OF ANTI-BETA-INTERFERON NEUTRALISING ANTIBODIES STATUS AND DISEASE SEVERITY IN A COHORT OF MULTIPLE SCLEROSIS PATIENTS

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Background: The impact of neutralising antibodies to beta-interferon in the treatment of patients with multiple sclerosis remains a controversial issue. The effect on disease progression and severity is less clear than that on relapse rate and MRI outcome measures. We aim to assess the effect of anti-beta-interferon neutralising antibodies status (NAB status) on disease severity, as measured by the Multiple Sclerosis Severity Score (MSSS).
Method: 90 patients with multiple sclerosis were interviewed, examined and serum sample taken for testing. NABS: 37 patients treated with Avonex, 20 with Betaferon and 33 with Rebif. Serum samples were tested by a novel cell based anti-beta-interferon neutralising antibodies assay based on interferon stimulated luciferase expression by human fibrosarcoma cells transfected with the firefly luciferase gene.
Results: Analysis of the first 45 samples showed that 5% of the Avonex group (1 of 20), 17.6% of the Rebif group (3 of 17) and 37.5% of the Betaferon group (3 of 8) developed neutralising antibodies of a titre of 20 or more. Mean MSSS score in the NAB positive patients (n = 7) was 2.61 whereas the mean MSSS score in the NAB negative group (n = 38) was 2.52. No significant difference was found in the mean MSSS between the two groups (p value 0.93, CI −2.3 to 2.1).

Initial results suggest no significant impact of neutralising antibodies to beta-interferon on disease severity, as measured by the Multiple Sclerosis Severity Score.

127 CATHEPSIN D POLYMORPHISMS AND COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

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Introduction: Cognitive disability in multiple sclerosis (MS) affects 45–60% of patients. A functional cathepsin D polymorphism, RS17571, has been linked with an increased risk of developing Alzheimer's disease. We examined three cathepsin D polymorphisms in MS patients to determine if there was a relationship between neuropsychological impairment and the cathepsin D gene.
Method: 194 unrelated Northern Europeans diagnosed with MS using the Poser Criteria underwent neuropsychological assessment. The battery of tests included the Wisconsin Card Sorting Test, Rey Auditory Verbal Learning Test, Judgment of Line Orientation, Controlled Oral Word Association and Symbol Digit Modalities Task. Tests were conducted to control for potential covariates. Three cathepsin D polymorphisms, RS17571, RS 2292962 and RS 2292963, were genotyped. Overall neuropsychological outcome was compared according to genotype using a multiple linear regression.
Results: The mean age of disease onset was 34 years with a mean duration of 15 years. The group consisted of 78% female and 22% male. There was no association between overall neuropsychological scores between patients with the RS17571 mutant T allele (n = 29) and those without (n = 163) (p = 0.45). No significant associations were observed for the other two single nucleotide polymorphisms.
Conclusion: There was no relationship between the cathepsin D polymorphisms and neuropsychological disability in MS patients.

128 THE USE OF CSF ANGIOTENSIN CONVERTING ENZYME IN DIAGNOSIS OF NEUROSARCOIDOSIS

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Sarcoidosis is associated with neurological disease in 5% of patients, a proportion of whom will have disease confined to the central nervous system only. MR scan appearances may be suggestive of neurosarcoid but are not specific, and the disease can present with atypical appearances. Histological confirmation is the gold standard for diagnosis but may be impossible.

The use of CSF angiotensin converting enzyme (ACE) in the diagnosis of neurosarcoid is still controversial but a few small studies suggest that it may be of use. In order to investigate this further, we assessed all patients who had undergone CSF ACE at Hope Hospital.

Of the 160 patients who had CSF ACE performed, CSF ACE was elevated in 15; 6 of these 15 (40%) patients had probable neurosarcoidosis.

Of the 12 patients identified with neurosarcoidosis, 6 had elevated CSF ACE (50%) compared with 7% of patients without neurosarcoid. The sensitivity of ACE for diagnosis of neurosarcoid was therefore 50%, and specificity was 93%.

Elevated CSF ACE was also seen in patients with spinal cord compression and tethering, chronic inflammatory demyelinating polyneuropathy, lymphoma and cerebrovascular disease.

This study shows that in the clinical situation, CSF ACE seems a useful adjunct to standard clinical tests in the diagnosis of neurosarcoidosis.

129 THE NEURAL SUBSTRATES OF IMPAIRED TAPPING REGULARITY AFTER STROKE: A 3 T FUNCTIONAL MRI STUDY

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The ability to fingertap in pace with external cues can be impaired after stroke, independently of tapping speed (Calautti, *Brain Res Bull* 2006).[1] However, the underlying neural substrates are unknown. Functional MRI (fMRI) in normal subjects suggests the dorsal premotor (PMd) and prefrontal (PFCx) cortices are involved during externally cued tapping.

Prospectively recruited right handed chronic stroke patients (n = 19, mean age 64 years), well recovered from left or right hemiparesis, performed fMRI during affected hand index–thumb tapping auditory cued at 1.25 Hz. Regularity index (RI) was measured during the same task using accelerometry.[1] The maximum number of index–thumb taps in 15 s (IT-Max) was also recorded. For fMRI analysis, lesions were flipped to the right hemisphere. Effect size compared with rest within the PMd and PFCx regions of interest was obtained.

Across the sample, the RI was reduced relative to the non-affected hand ($p = 0.08$). RI scores were negatively correlated with the left PMd such that the worse the RI the greater the activation ($p = 0.000$, FDR corrected), and positively with the left PFCx ($p = 0.04$, FDR corrected)—that is, the better the RI the greater the activation. These correlations remained significant after adding IT-Max as covariate.

Impaired tapping regularity after stroke appears to relate to both increased (?compensatory) PMd recruitment and impaired (?attentional) PFCx activation, both contralesionally.

130 EEG IN ANTICONVULSANT INDUCED ENCEPHALOPATHY

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We present a case report and EEG images of an 18-year-old woman who was admitted for seizure control. She had generalised tonic–clonic and absence seizures and had been on various antiepileptic medications. Her frequency of seizures was variable but seemed to increase while on sodium valproate 1500 mg twice daily and leviteracetam 1000 mg twice daily. She insisted that she was fully drug compliant.

The EEG 2 days into admission was in keeping with mild diffuse encephalopathy. Two days later, the background remained slow, but there were frequent sharp components. Intravenous lorazepam improved the slowing. Ammonia level was 38 μmol/l but sodium valproate was high (154 mg/l). Reduction in sodium valproate dose resulted in clinical and electrophysiological improvement.

This case highlights the dangers of non-compliance and the usefulness of checking levels in selected cases. Ammonia levels can be normal in the setting of valproate encephalopathy. Intravenous benzodiazepines, previously reported not to change background EEG activity in valproate encephalopathy (Ebersole and Pedley),[1] clearly did in this case. Anticonvulsant medication at toxic levels can produce an EEG which is difficult to differentiate from a non-convulsive epileptic state.

131 KEY STEPS TO DELIVERY OF A PERSON CENTRED RELAPSE SERVICE

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In the, UK 10 000 multiple sclerosis relapses occur per annum, often accompanied by significant disruption of day to day life for the individual and their family, which can take weeks or months to resolve. The essential components of effective relapse management are rapid specialist assessment (medical, nursing and therapy), coupled with intravenous corticosteroid delivery, in the context of an appropriate assessment of the total process.[1] Together with the Multiple Sclerosis Trust, and with consultation of interested centres around the UK, we have brought together a document which acts as a toolkit for the establishment and effective implementation of such a service.[2] The major topic headings are: audit and service evolution, clinical roles, clinical governance and finance. While reinforcing that secondary care is vital in assuring that correct pathways are used and quality maintained, it underlines the fact that treatment delivery can be given in a generalist environment by primary care services and outlines how this should be supported and measured. It has been forwarded to the National Services Framework as an example of good practice within the NHS.

132 EVALUATION OF ANTI-INTERFERON BETA ANTIBODIES IN SUBJECTS WITH MULTIPLE SCLEROSIS ATTENDING THE NATIONAL HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, LONDON

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Treatment with interferon-beta (IFNβ) is known to induce anti-interferon-β neutralising antibodies (NABS). The frequency of NABS depends on the IFNβ product, treatment duration and assay method. Accepted NAB frequencies are 2–6% Avonex, 20–35% Rebif and 30–45% Betaferon.

Our aim was to assess the frequency of NABS in subjects treated with IFNβ attending the National Hospital for Neurology and Neurosurgery, London, using novel reporter gene assay and to compare these results with published data. Participants with multiple sclerosis taking IFNβ for $\geqslant$2 years were studied. Serum samples at 12 and 24 months were tested for binding antibodies (capture ELISA) and then for neutralising activity (luciferase assay). A titre >20 TRU was considered positive. Charts were reviewed retrospectively for data regarding relapses and side effects.

327 subjects were included. Overall, 40% were binding antibody positive and 27% were NAB positive at any time. Risk at 12 months for being NAB positive was: Avonex 8%, Betaferon 39% and Rebif 33% ($p<10^{-5}$); at 24 months the risk was 8%, 31% and 27%, respectively ($p = 0.002$). Relapses were higher in NAB positive subjects (0.5 vs 0.67/year; $p = 0.04$). Side effects were associated with NAB negative status (non-significant). These results are comparable with the published literature, Avonex being the least immunogenic, and small difference between Rebif and Betaferon.

133 THE IMPACT OF FOCAL BRAIN DAMAGE ON INTELLIGENCE: CRITICAL REGIONS

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A cardinal question in neuroscience is what brain areas are critical to the most distinctively human capacity—intelligence. For various methodological reasons, functional imaging cannot answer this question but the study of patients with focal lesions can.

However, lesion mapping in neurological populations is complicated: technically by the need for laborious and subjective lesion tracing and theoretically by the complexity of lesion distributions. Therefore, little progress has been made.

Here we present a completely new framework for making spatial inferences from lesioned brains that overcomes these difficulties, and proceed to apply it to a large cohort of stroke patients (n = 124) with detailed MRI and neuropsychological data.

We show that the critical region predictive of a drop in IQ compared with premorbid estimates is within the anterior prefrontal cortex. Such investigation of neurological patients has the potential to provide an important contribution to key scientific questions and to guide the management of disorders associated with cognitive dysfunction.